



**GREAT FOR
USMLE® STEP 1
REVIEW!**

Microbiology & Infectious Diseases Flashcards



THIRD EDITION

**More than 100 high-yield cards
with a clinical case on every
disease-specific card**

Kenneth D. Somers • Stephen A. Morse • Molly A. Hughes

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Lange® Flashcards: Microbiology & Infectious Diseases

Third Edition

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UTI—fungal and parasites
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Preface

Lange Flashcards: Microbiology & Infectious Diseases is a strategy for learning medical microbiology in the context of a case vignette highlighting a common clinical problem. This unique approach is highly relevant in reviewing for the USMLE Step 1 examination because Step 1 examination questions are framed in a clinical context. These cards provide the most complete, concise, and high-yield information for the major microbial diseases caused by bacteria, viruses, fungi, and parasites. The basic and introductory cards in each chapter describe the basic principles of each major group of organisms and the key concepts of the various groups of infectious agents. Each disease-specific card contains a clinical vignette on one side and important characteristics of the causative organism and disease on the reverse side. Information is brief and organized into sections entitled disease or clinical syndrome, etiology and epidemiology, clinical manifestations, pathogenesis, laboratory diagnosis, and treatment and prevention. High-yield information is highlighted in **bold type** for ease of review. The last chapter consists of tables that depict the role of medically important bacteria, viruses, fungi, and parasites in major infectious disease syndromes. These cards should be a powerful and useful adjunct to medical microbiology courses and board-review textbooks in preparation for the USMLE Step 1 examination.

STRUCTURE

- Cell wall

Bacteria have two basic cell envelope structures differentiated on the basis of the Gram stain that are referred to as gram positive and gram negative.

The **gram-positive** cell envelope consists of a cytoplasmic membrane comprised of phospholipids and proteins, surrounded by a thick, highly cross-linked layer of **peptidoglycan**. Other components may include **teichoic acids**, **lipoteichoic acids**, and various surface proteins.

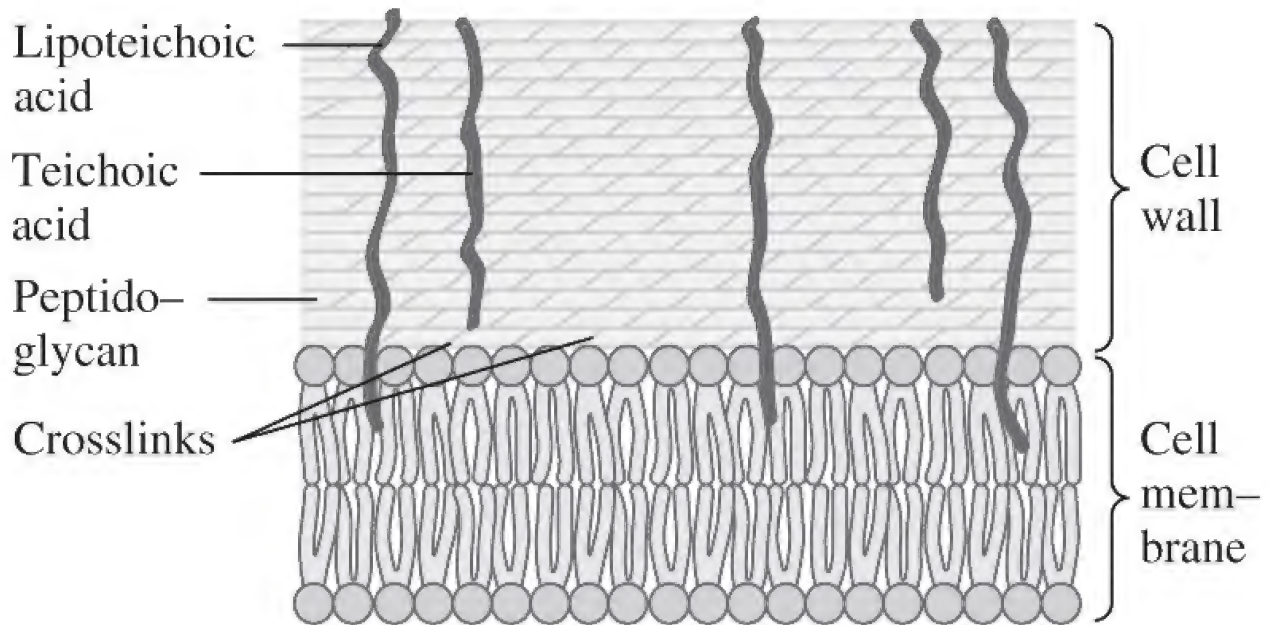
The **gram-negative** cell envelope consists of an inner cytoplasmic membrane, a thin layer of peptidoglycan that is lightly crosslinked, a periplasmic space, and an outer membrane. The outer membrane is an asymmetric bilayer with a glycolipid (ie, lipopolysaccharide [LPS]) in its outer leaflet. LPS, also known as endotoxin, consists of three parts: lipid A, a core polysaccharide, and “O” polysaccharide repeat units. Some gram-negative bacteria have glycolipids that lack O-antigens and are termed lipooligosaccharides (LOS).

Peptidoglycan is a complex polymer consisting of a backbone of alternating *N*-acetyl-glucosamine and *N*-acetylmuramic acid; a set of identical tetrapeptide side chains attached to *N*-acetylmuramic acid; and a set of identical peptide cross-links. The specific cross-link is between a terminal **d - alanine** of one side chain and the **diamino-containing amino acid** (lysine or diaminopimelic acid) of a second side chain. The tetrapeptide side chains and peptide cross-bridges vary from species to species. Penicillin-binding proteins, also known as **transpeptidases**, catalyze the cross-linking reaction and are the targets of beta-lactam antibiotics. Cross-linking can be direct or indirect through a peptide (eg, **pentaglycine**) bridge.

- Other important cell envelope structures include **pili** or **fimbriae**, **flagella**, and **capsules**.

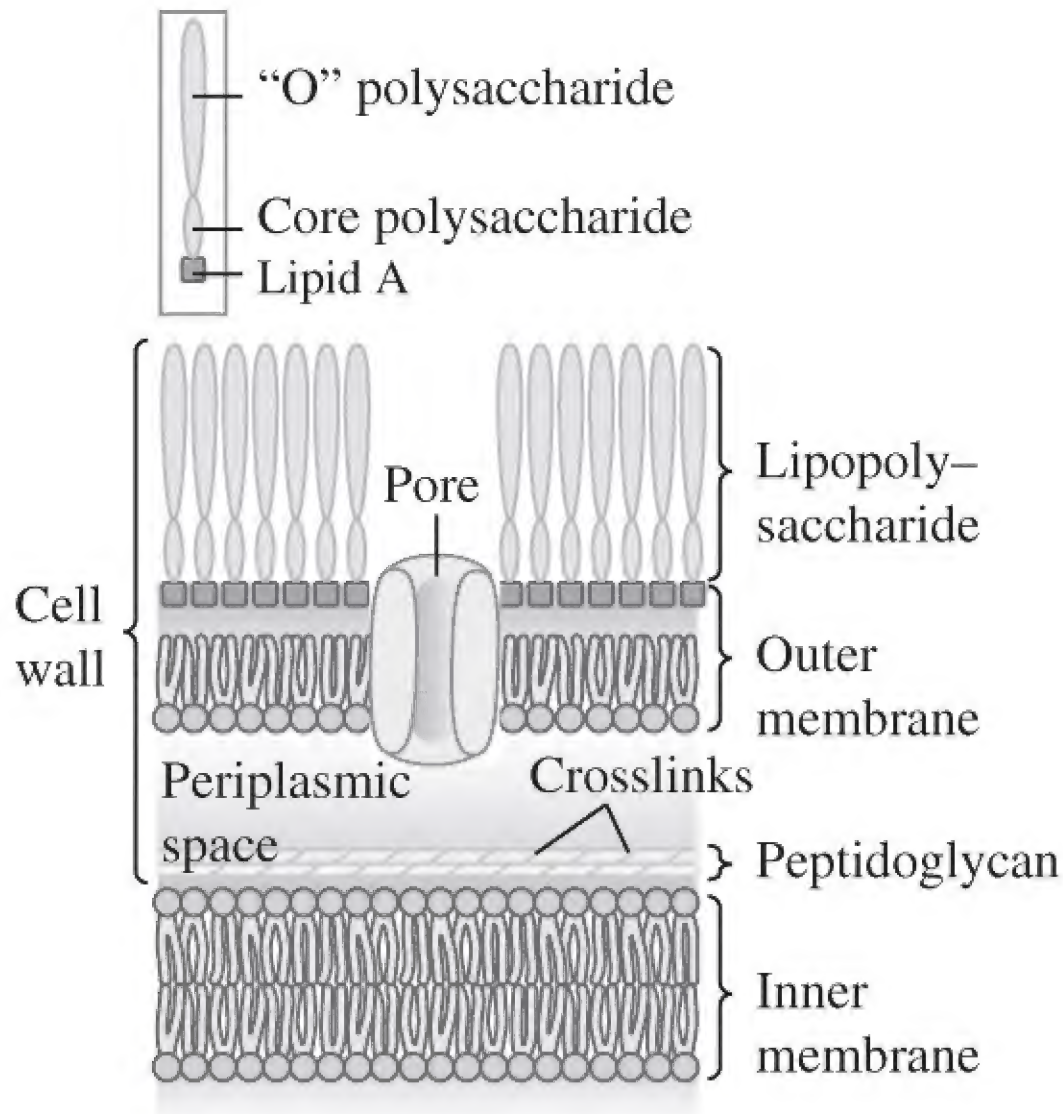
NOTES

GRAM-POSITIVE CELL ENVELOPE



The gram-positive cell envelope. Structural features include a thick layer of highly cross-linked peptidoglycan, teichoic acids, lipoteichoic acids, and a cell (cytoplasmic) membrane.

GRAM-NEGATIVE CELL ENVELOPE



The gram-negative cell envelope. Structural features include an inner (cytoplasmic) membrane, a thin layer of peptidoglycan that is lightly cross-linked, and an outer membrane. The outer membrane is an asymmetric bilayer in which the outer layer consists of lipopolysaccharide and proteins, some of which form pores. Lipopolysaccharide has three major components—lipid A, core polysaccharide, and “O” polysaccharide.

GENETICS

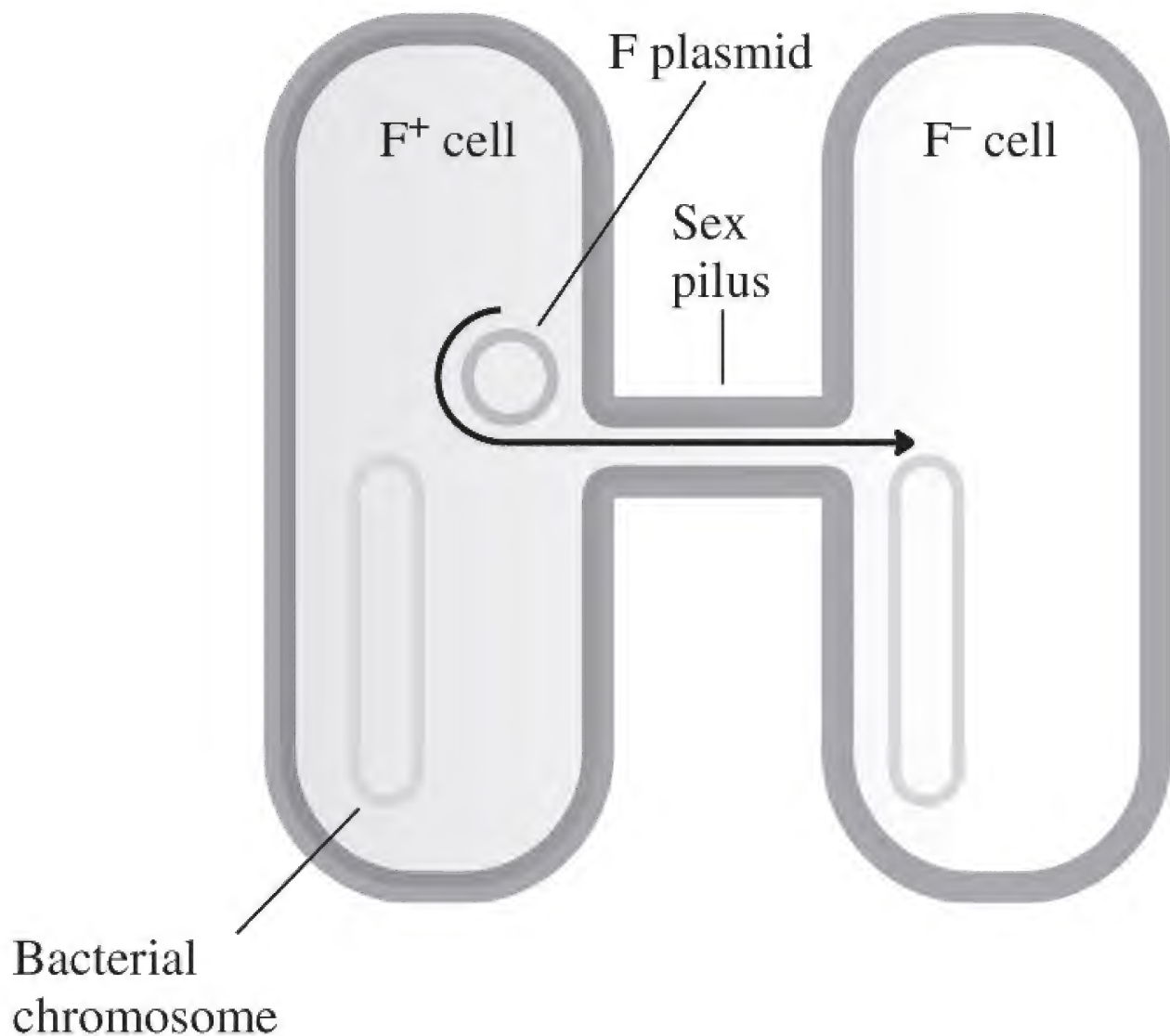
Bacteria have no true nucleus. The genome of most bacteria consists of a single (haploid) circular chromosome (a few have two circular chromosomes or a linear chromosome). Some bacteria also contain extrachromosomal circular DNA in

the form of self-replicating plasmids. Plasmids often carry virulence genes and antibiotic resistance genes.

Genetic variation occurs by two general mechanisms: **mutation** and **gene transfer**.

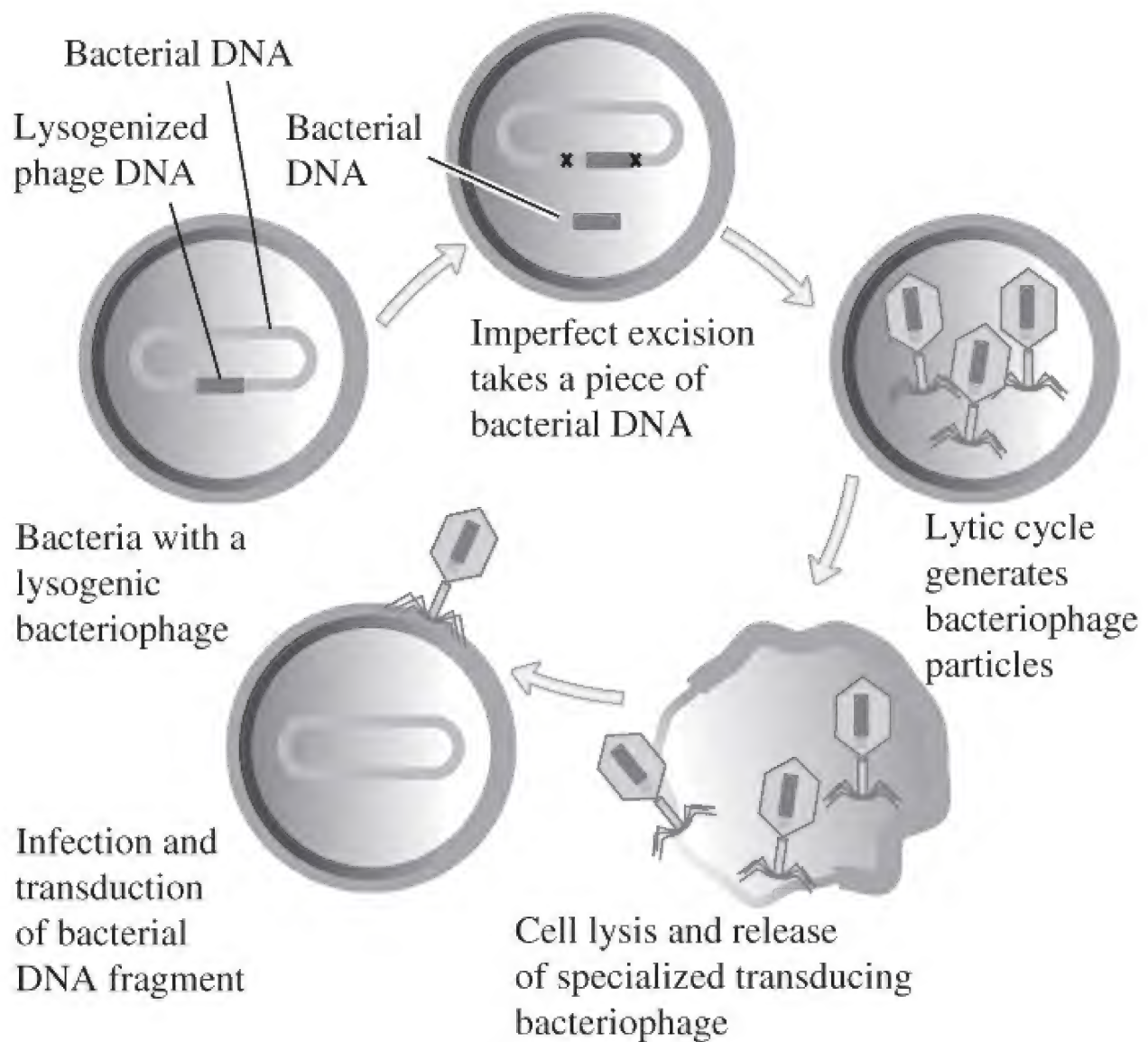
- Spontaneous mutation occurs at random and at low frequency. Genotypic variation always occurs, but phenotypic variation depends on the specific mutational event and environmental conditions. Phenotypic changes are either gain of function or loss of function.
- Gene transfer occurs by four major mechanisms. The result is the acquisition of new genetic information which can affect multiple traits. Gene transfer can occur rapidly and at high frequency. The major mechanisms are **transformation, transduction, conjugation, and transposition**.
 - ▶ **Transformation** is the uptake of free DNA by competent living bacteria. Some organisms, including *Streptococcus pneumoniae* and *Neisseria* species, are naturally competent for this type of gene transfer.
 - ▶ **Conjugation** is the transfer of genetic information from one living bacterium to another during direct contact. Transfer is mediated through a specialized **sex pilus** encoded by *Tra* genes. The *Tra* genes are generally carried on an F (fertility) plasmid. An F⁺ cell mates with an F⁻ cell, resulting in both cells becoming F⁺. Other plasmids can also be transferred during conjugation through a process called **mobilization**.
 - ▶ **Transduction** is bacteriophage-mediated gene transfer. **Lysogeny** is the process by which bacteriophage DNA becomes incorporated into the bacterial chromosome. Many virulence factors are carried by lysogenic bacteriophages. Lysogenized phage can be **induced** to undergo a **lytic cycle**, which perpetuates spread. Transduction can be **generalized** or **specialized**. In specialized transduction, a piece of bacterial DNA is carried on a replication-competent bacteriophage.
 - ▶ **Transposition** is the process by which pieces of DNA are able to physically move from one location to another. These movable DNA pieces are called **transposons** and can carry a variety of virulence factors. Transposons are not self-replicating and their propagation requires their physical integration with the bacterial chromosome.

CONJUGATION



Conjugation. A bacterium containing an F plasmid is considered to be a male cell. The *Tra* genes on the F plasmid initiate sex pilus formation; during replication a copy of the F plasmid is transferred to an F^- recipient cell. Following transfer, the F^- cell becomes F^+ .

SPECIALIZED TRANSDUCTION



Specialized transduction. A bacterium containing a lysogenized bacteriophage is induced to undergo a lytic cycle. On induction, the phage DNA is imperfectly excised from the bacterial chromosome. The phage DNA containing a sequence bacterial DNA is packaged into phage particles. The cell is lysed, and bacteriophages infect new cells.

MECHANISMS OF PATHOGENESIS

Bacteria carry a variety of virulence factors that facilitate pathogenesis. These include factors that help them evade the immune system, factors that facilitate adhesion, factors that facilitate spread through tissues and invasion of host cells,

and a variety of different toxins that are toxic to host cells.

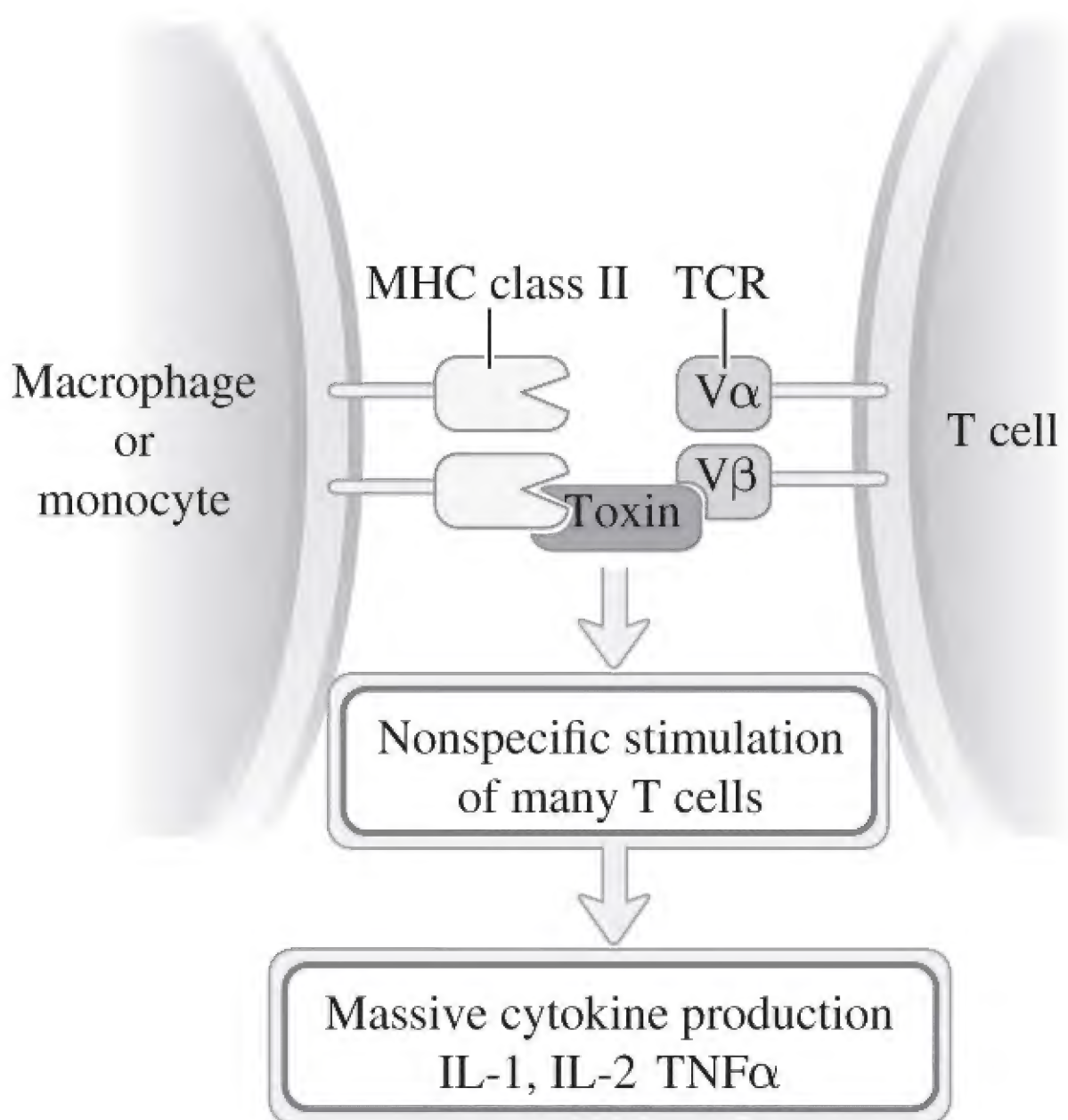
- Factors that help bacteria evade the host immune system:
- Structural components like capsules prevent phagocytosis.
 - ▶ A variety of proteins, such as listeriolysin O, facilitate intracellular survival in phagosomes.
 - ▶ Enzymes involved in destruction of immune molecules include IgA proteases and leukocidins.
 - ▶ Antigenic variation and phase variation result in a change of surface antigens effectively allowing bacteria to hide from preformed antibody.
 - ▶ Intracellular invasion allows bacteria to evade the humoral immune response.
- Factors that facilitate adhesion, invasion, and spread include flagella, pili, cell wall–associated proteins, slime layers, and enzymes including hyaluronidase, mucinase, and urease.
- Two general types of bacterial toxins are common. LPS, which is extremely toxic to animals, has been called the endotoxin of gram-negative bacteria because it is an integral part of the cell wall and is released only when the cells are lysed. When LPS is split into lipid A and polysaccharide, all of the toxicity is associated with the lipid A component. Endotoxin stimulates inflammatory cytokines including tumor necrosis factor alpha and interleukin-1 (IL-1). Many different exotoxins can be produced that affect a variety of cellular processes including inhibition of protein synthesis; others have adenylate cyclase activity or function as superantigens. Some toxins are neurotoxins or cytotoxins.

NOTES

EXAMPLES OF BACTERIAL EXOTOXINS

Protein Synthesis Inhibitors	Adenylate Cyclase Activity	Superantigens Stimulation	Neurotoxins	Cytotoxins
Shiga toxin	Cholera toxin	TSST-I	Botulinum	Alpha toxins (eg, <i>S. aureus</i> , <i>C. perfrin- gens</i>)
Diphtheria toxin	<i>Escherichia coli</i> heat- labile enterotoxin	<i>Group A Streptococcus pyogenic</i> exotoxins	Tetanus	Streptolysins
<i>Pseudomonas</i> exotoxin A	Pertussis toxin	Staphylococcal enterotoxins		
	Anthrax edema toxin	Staphylococcal exfoliatin toxin		Anthrax lethal toxin

SUPERANTIGEN TOXINS



Some bacterial toxins are superantigens. Superantigens bind distinct regions outside the peptide-binding cleft of the major histocompatibility complex (MHC) class II molecules on antigen-presenting cells and bridge with the V β component of the T-cell receptor (TCR), causing nonspecific proliferation of peripheral T cells and the concomitant production of massive amounts of inflammatory cytokines (eg, IL-1, IL-2, IL-6, TNF α , γ -interferon).

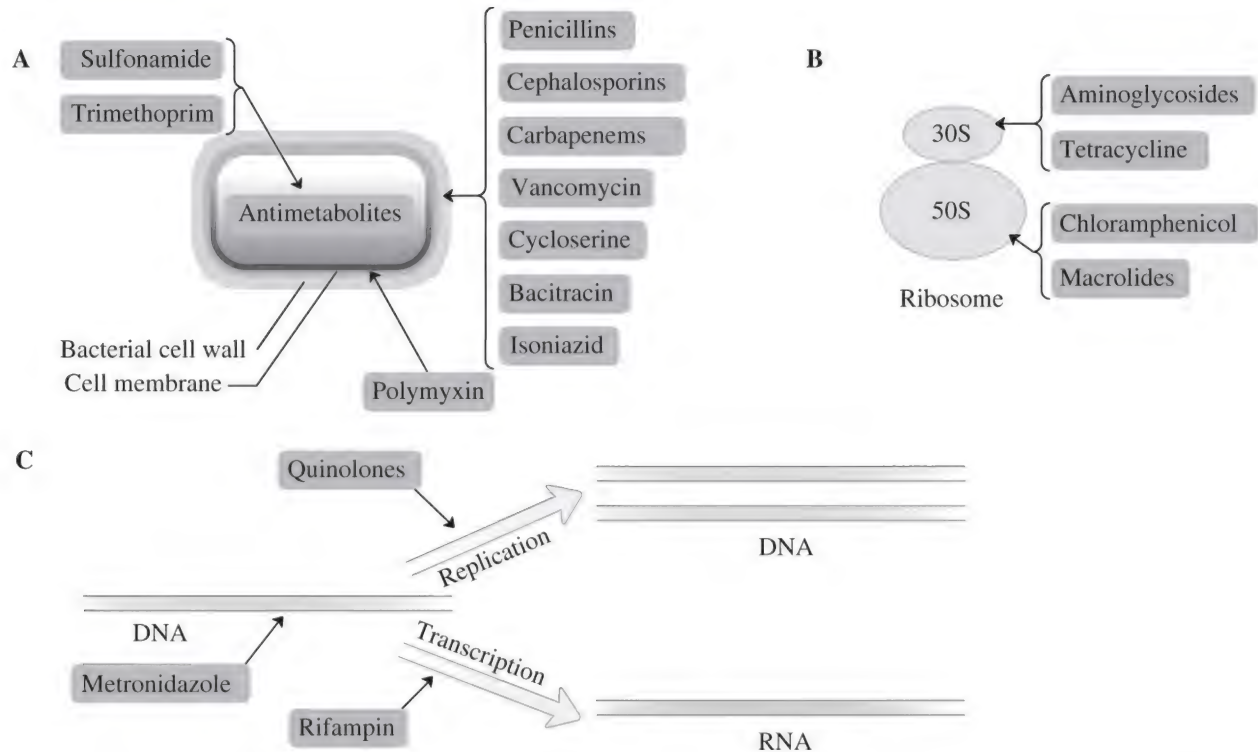
MECHANISMS OF ANTIBIOTIC ACTION

Antibiotics exploit the differences between prokaryotic and eukaryotic cells to promote specificity and limit toxicity. For example, bacterial enzymes involved in DNA replication and RNA synthesis are different from those found in eukaryotic cells. The bacterial ribosome is also significantly different, allowing selective targeting. One of the major differences between bacteria and eukaryotic cells is the peptidoglycan-containing bacterial cell wall whose synthesis is inhibited by several antibiotics. Antibiotics target bacteria by five major mechanisms:

- Inhibition of cell wall synthesis.
 - ▶ β -lactam antibiotics such as **penicillins**, **cephalosporins**, and **carbapenems** target peptidoglycan cross-linking by binding to and inhibiting the action of the transpeptidase enzymes. **Vancomycin** inhibits cross-linking by binding the terminal D-alanine-D-alanine precursor and preventing transpeptidation. **Cycloserine** inhibits the formation of the D-alanine-D-alanine linkage. **Bacitracin** inhibits transport of new peptidoglycan precursors through the cell membrane. **Isoniazid** and **ethionamide** inhibit mycolic acid (a cell envelope component) synthesis in mycobacteria.
- Inhibition of protein synthesis.
 - ▶ **Aminoglycosides** such as streptomycin, neomycin, and kanamycin irreversibly bind and inhibit the function of the 30S ribosomal subunits. **Tetracyclines** reversibly inhibit the binding of aminoacyl tRNA to the 30S subunit. **Macrolides** such as erythromycin, azithromycin, and clarithromycin attach to a 23S RNA on the 50S subunit. **Chloramphenicol** blocks the attachment of amino acids to the nascent peptide chain on the 50S subunit.
- Inhibition of nucleic acid synthesis.
 - ▶ **Quinolones** and **fluoroquinolones** such as ciprofloxacin inhibit DNA synthesis by blocking DNA gyrase. **Rifampin** binds strongly to DNA-dependent RNA polymerase and thus inhibits RNA synthesis. **Metronidazole** interacts with DNA altering its helical structure and causing DNA fragmentation.
- Alterations of cellular membranes.
 - ▶ Polymyxins (eg, colistin) target cell membranes rich in phosphatidylethanolamine, causing an increase in cellular permeability.
- Antimetabolites.

- Sulfonamides and trimethoprim inhibit folic acid metabolism.

ANTIBIOTIC ACTION



Mechanisms of antibiotic action. **A:** Schematic showing cell wall-active, membrane-active, and cytoplasm-active antimicrobial agents. **B:** Antibiotics that inhibit protein synthesis by interacting with different ribosome subunits. **C:** Antibiotics that inhibit nucleic acid synthesis.

MECHANISMS OF ANTIBIOTIC RESISTANCE

Bacteria have evolved a number of mechanisms to protect themselves from the action of antibiotics. Often the genes encoding antibiotic resistance are carried on transposons and plasmids, and are therefore easily transferred from one organism to another, creating bacteria that are resistant to multiple antibiotics.

Four major mechanisms are involved.

- Inactivation of the antibiotic through hydrolysis (eg, β -lactamases that cleave the β -lactam ring of penicillins, cephalosporins and carbapenems).

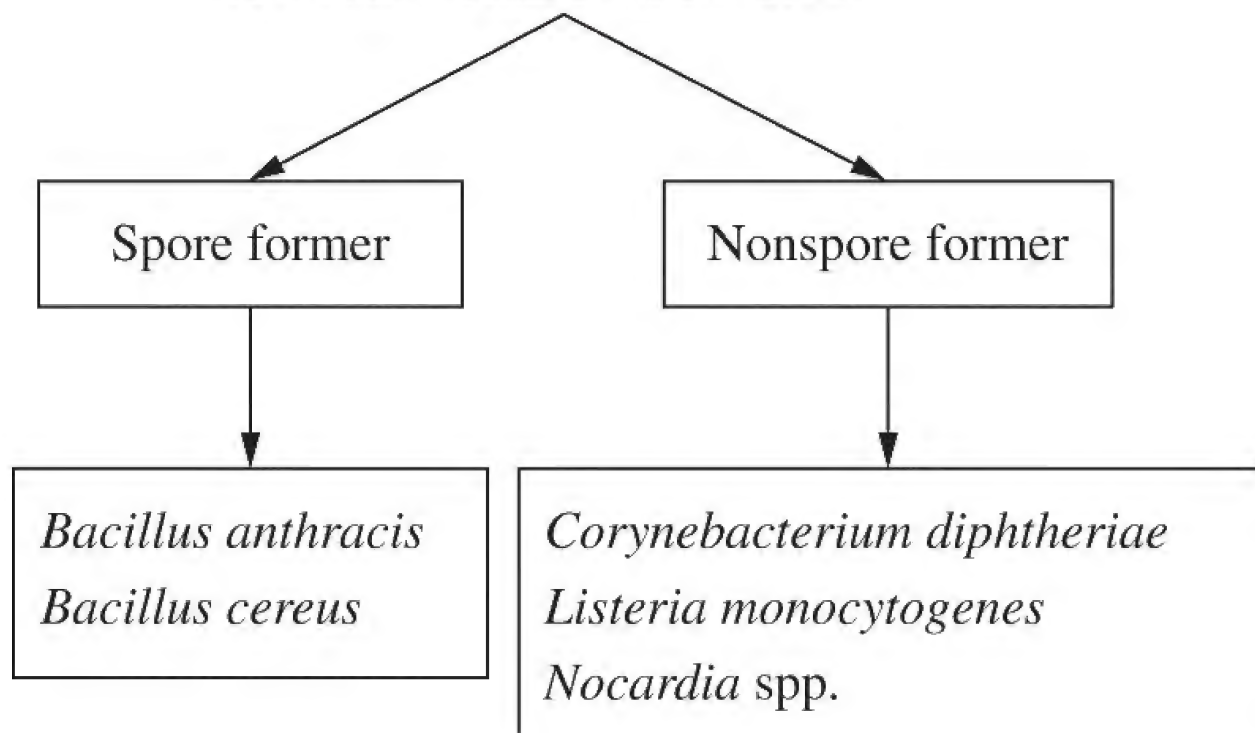
- Chemical modification of the antibiotic through acetylation, phosphorylation, or adenylation (eg, chloramphenicol acetyl transferase that transfers an acetyl group from acetyl CoA to chloramphenicol, resulting in its inactivation).
- Alteration of antibiotic targets through mutation (eg, the alteration of a single amino acid in ribosomal protein S12, which prevents streptomycin binding to the 30S ribosome subunit without affecting protein synthesis).
- Alterations that affect permeability (ie, decrease the intracellular concentration of antibiotic) are used by a variety of antibiotics. This can involve a decreased influx or an increased efflux from the bacterial cell.

NOTES

MECHANISMS OF ANTIBIOTIC RESISTANCE

Antibiotic	Antibiotic Hydrolysis	Antibiotic Modification	Altered Target	Altered Permeability, Influx, or Efflux
Penicillins	+		+	+
Cephalosporins	+		+	+
Carbapenems	+			
Vancomycin			+	+
Cycloserine			+	+
Isoniazid			+	+
Bacitracin				+
Aminoglycosides		+	+	+
Tetracyclines		+	+	+
Chloramphenicol		+		
Macrolides			+	+
Fluoroquinolones			+	+
Rifampin			+	+
Metronidazole				+
Sulfonamides/trimethoprim			+	+
Polymyxins			+	

Aerobic Gram-Positive Rods



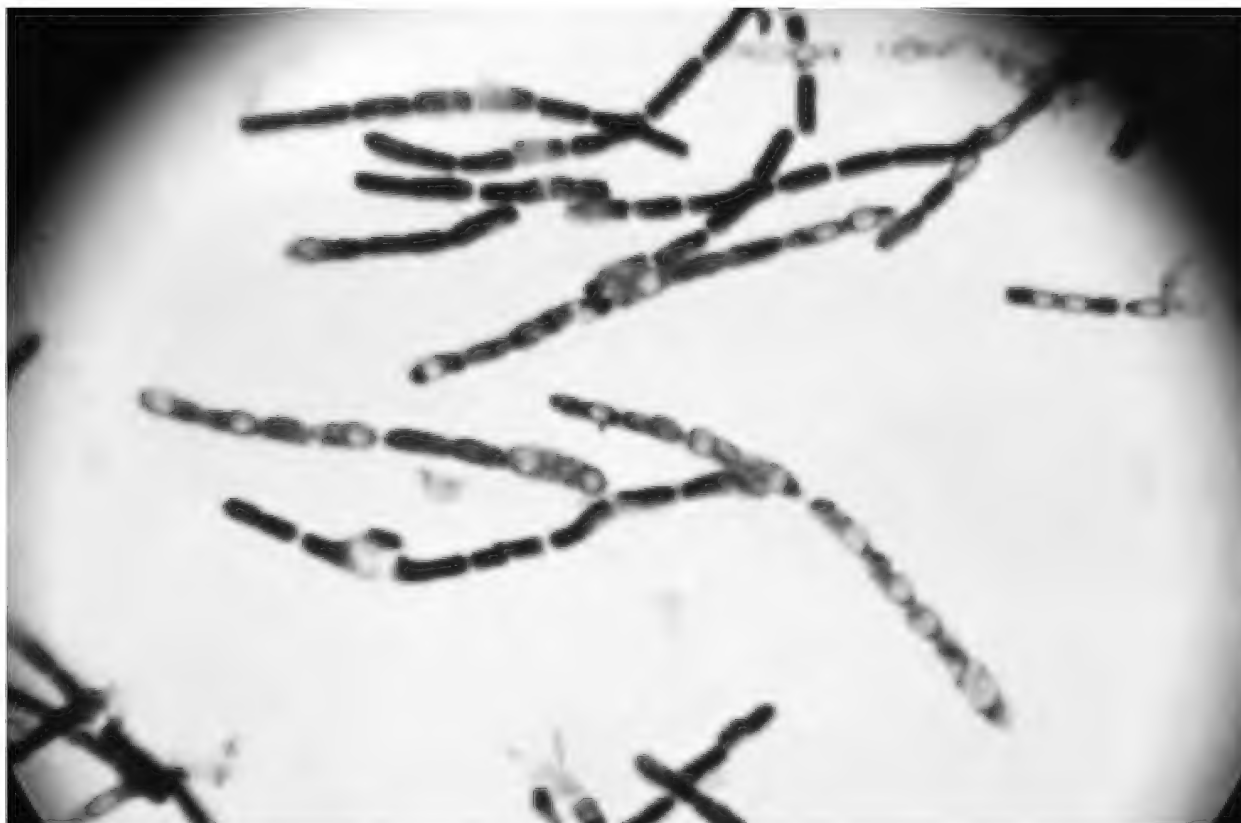
KEY CONCEPTS

- These organisms are infrequent causes of human diseases in developed countries. These diseases occur more frequently in developing countries. Some of these bacteria are highly pathogenic.

SUMMARY OF VIRULENCE FACTORS OF AEROBIC GRAM-POSITIVE RODS

Organism	Virulence Factor
<i>Bacillus anthracis</i>	Capsule of D-glutamic acid 2 exotoxins: protective antigen (PA) + edema factor (EF) = edema toxin (ET) PA + lethal factor (LF) = lethal toxin (LT)
<i>Bacillus cereus</i>	Heat-labile enterotoxin Heat-stable emetic toxin
<i>Corynebacterium diphtheriae</i>	Diphtheria toxin
<i>Listeria monocytogenes</i>	Listeriolysin O Internalin
<i>Nocardia</i> spp.	Not well characterized

A 35-year-old rancher presents with complaints of an ulcerated lesion on the back of his hand that has turned black and necrotic. Although the lesion does not hurt, his hand is swollen and he has recently developed a fever and headache. Questioning reveals that several of the patient's cattle have died recently from unknown causes.



Source: Centers for Disease Control and Prevention, Washington, DC.

Cutaneous Anthrax

Organism and Physical Characteristics:	<i>Bacillus anthracis</i> Disease: Anthrax. Gram-positive rod, end-to-end chains, forms endospores.
Etiology and Epidemiology	Anthrax is transmitted through contact with spores. Primarily a disease of animals, human infection (zoonoses) can occur following contact with infected animals or animal products (eg, hides). Spores may remain viable for years in the environment.
Clinical Manifestations	Four forms of anthrax are recognized based on the site of inoculation. Cutaneous , the most common form, causes a localized inflammatory black necrotic lesion (eschar). Inhalation is highly fatal and characterized by rapid and massive edema in the chest followed by cardiovascular shock. Gastrointestinal resulting from ingestion of spores is rare but also highly fatal. Injectional occurs in drug users who inject contaminated heroin.
Pathogenesis	Major virulence factors: edema toxin (EF + PA), lethal toxin (LF + PA), and a capsule of D-glutamic acid. PA binds the anthrax toxin receptor on the surface of host cells and facilitates the translocation of EF and LF into the cell. EF is an adenylate cyclase that increases intracellular cAMP, stimulating an efflux of fluids and ions that results in edema. LF is a mitogen-activated protein kinase kinase (MAPKK) protease that disrupts cell signaling, causing cell death and tissue necrosis.
Treatment and Prevention	Antibiotics such as ciprofloxacin, doxycycline, or cephalosporins have been used for treatment of susceptible vegetative organisms. Suspected exposures to spores are often treated with a long course (60 days) of antibiotics such as ciprofloxacin. A variety of antitoxin strategies are currently in development. Vaccination with the anthrax vaccine adsorbed (AVA) vaccine targets the PA toxin subunit and is given as 5 injections over 18 months with yearly boosters.

One hour after dinning on sweet and sour pork and pork fried rice at a local Chinese restaurant, an 18-year-old college freshman exhibits abdominal discomfort and nausea and then begins vomiting. Her roommate suspects that it is something she ate, and takes her to the campus health center. After determining that the symptoms were not alcohol induced, she is treated symptomatically.

Food Poisoning

Organism and Physical Characteristics:	<i>Bacillus cereus</i> Disease: Food poisoning, eye infections, intravenous catheter infections. Gram-positive rod, forms endospores.
Etiology and Epidemiology	Food poisoning is by “ intoxication. ” Spores survive usual cooking temperatures and germinate when food is left at room temperature. <i>B. cereus</i> produces two different toxins: heat-labile enterotoxin and heat-stable emetic toxin. The heat-labile toxin is associated with contaminated meats and vegetables. The heat-stable toxin is associated with fried rice.
Clinical Manifestations	Food poisoning symptoms include watery diarrhea —which can occur 6 to 24 hours after ingestion of contaminated meats, poultry, or vegetables—and vomiting , which may occur 1 to 6 hours after ingestion of contaminated fried rice. Opportunistic infections include traumatic eye and intravenous catheter-related infections.
Pathogenesis	The heat-labile toxin stimulates cellular adenylate cyclase, leading to an elevation of cAMP and watery diarrhea. The heat-stable toxin stimulates vomiting through an unknown mechanism.
Treatment and Prevention	Food poisoning is treated with fluid replacement. Blood and eye infections often require intravenous vancomycin because of resistance to multiple antibiotics. Food poisoning can be prevented through proper food handling such as refrigeration and heating foods above 56°C before eating (heat-labile toxin).
Notes	

A 3-year-old boy is brought to the hospital with a sore throat, fever, malaise, and difficulty breathing. Physical examination reveals the presence of a gray membrane covering the pharynx. Questioning of the mother reveals that the boy had not received any vaccinations.



Source: Centers for Disease Control and Prevention, Washington, DC.

Diphtheria

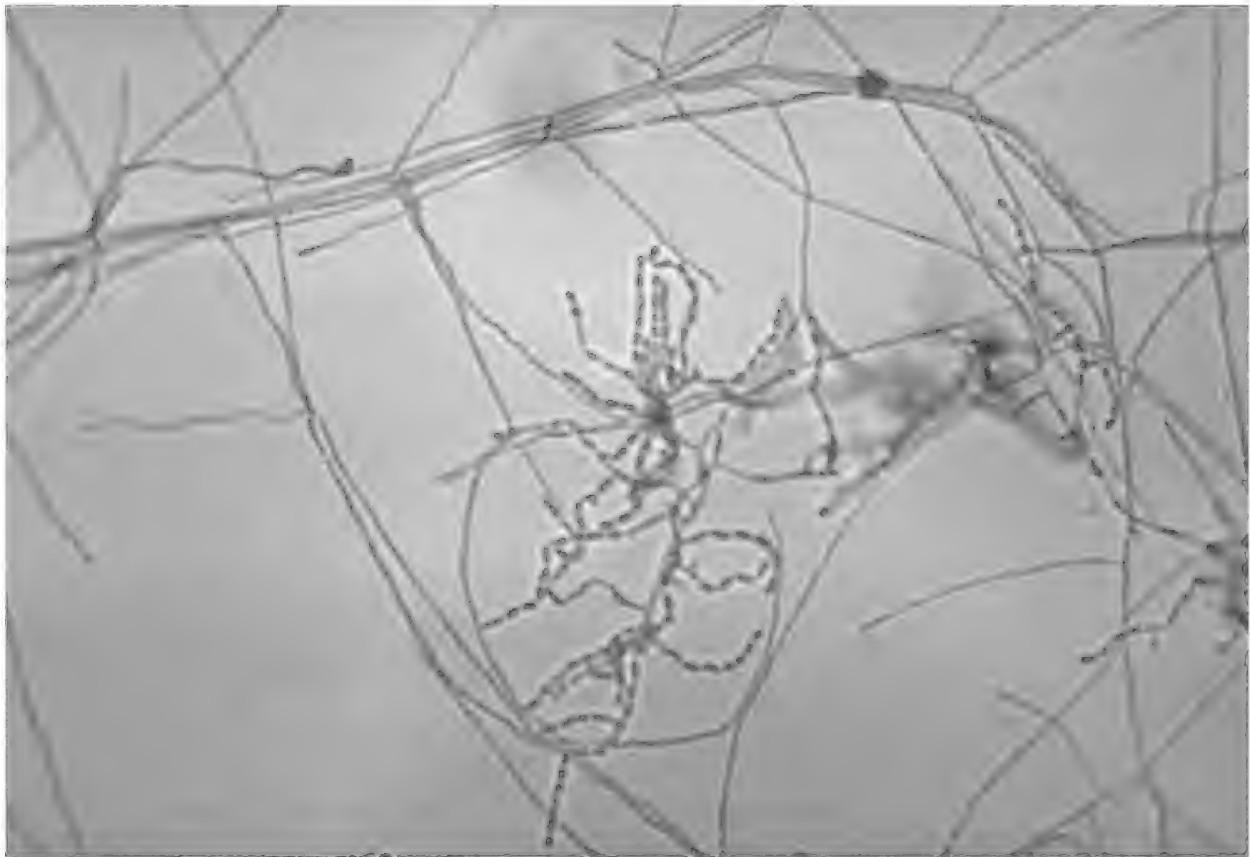
Organism and Physical Characteristics:	<i>Corynebacterium diphtheriae</i> Disease: Diphtheria. Gram-positive rod, pleomorphic.
Etiology and Epidemiology	Humans are the natural host. Transmission is by respiratory droplets.
Clinical Manifestations	A prominent feature of nasopharyngeal diphtheria is the presence of a pseudomembrane comprised of necrotic cells, fibrin, and bacteria. The pseudomembrane serves as a platform for bacterial growth and toxin production. Death can result from mechanical obstruction of the airway or by toxin-induced myocardial and neurologic damage.
Pathogenesis	The major virulence factor is an exotoxin called diphtheria toxin. The diphtheria toxin is an A-B toxin that ADP ribosylates translation elongation factor 2 (EF2), resulting in shutdown of protein synthesis and cell death.
Treatment and Prevention	Treatment includes a combination of antitoxin administration and antibiotics such as penicillin or erythromycin. Diphtheria is effectively controlled by immunization with an inactivated toxin (diphtheria toxoid).
Notes	

A 45-year-old man presents to his oncologist with fever, headache, and stiff neck. He has been undergoing chemotherapy for the last 4 months for advanced-stage colon cancer. A lumbar puncture reveals numerous neutrophils and gram-positive rods. He is admitted to the hospital and started on IV ampicillin and gentamicin.

Listeriosis

Organism and Physical Characteristics:	<i>Listeria monocytogenes</i> Disease: Listeriosis. Gram-positive rod, tumbling motility, growth at low temperatures.
Etiology and Epidemiology	Transmission is from ingestion of contaminated foods and through person-to-person spread. Food contamination is accentuated by the organism's ability to grow at refrigerator temperatures. Sources of infection include contaminated meats, cheese, milk, poultry, and seafood. Person-to-person spread can occur through in utero infections, colonization of the birth canal, and nosocomial transmission by hospital workers.
Clinical Manifestations	There are three categories of listeriosis. Perinatal listeriosis can manifest as meningitis, pneumonia, or septicemia, with severe cases resulting in stillborn births, spontaneous abortion, or an overwhelming disease called granulomatosis infantiseptica. Asymptomatic infections can occur in immunocompetent adults including pregnant women. Adult bacterial meningitis and other invasive infections caused by <i>Listeria monocytogenes</i> are rare in healthy adults but common in individuals who are immunocompromised from cancer chemotherapy, transplants, or HIV infection.
Pathogenesis	The major pathogenic mechanism involves host cell invasion. This is facilitated by two virulence factors, internalin and listeriolysin O. Internalin binds to host cells and promotes endocytosis. Listeriolysin O is a pore-forming toxin that allows organisms to escape from the endosome. <i>L. monocytogenes</i> replicates in the cytoplasm and spreads to adjacent cells, thus escaping the humoral immune response. Transplacental spread is mediated by invasion of placental endothelial cells from a bacteremia in an asymptomatic pregnant woman. Immunity is primarily cell-mediated.
Treatment and Prevention	<i>Listeria</i> infections can be treated with a variety of antibiotics including ampicillin +/- aminoglycosides, or in the penicillin allergic patient, trimethoprim sulfamethoxazole. Infection control involves elimination of animal reservoirs, care in handling infants, and early diagnosis and treatment of infected pregnant women.

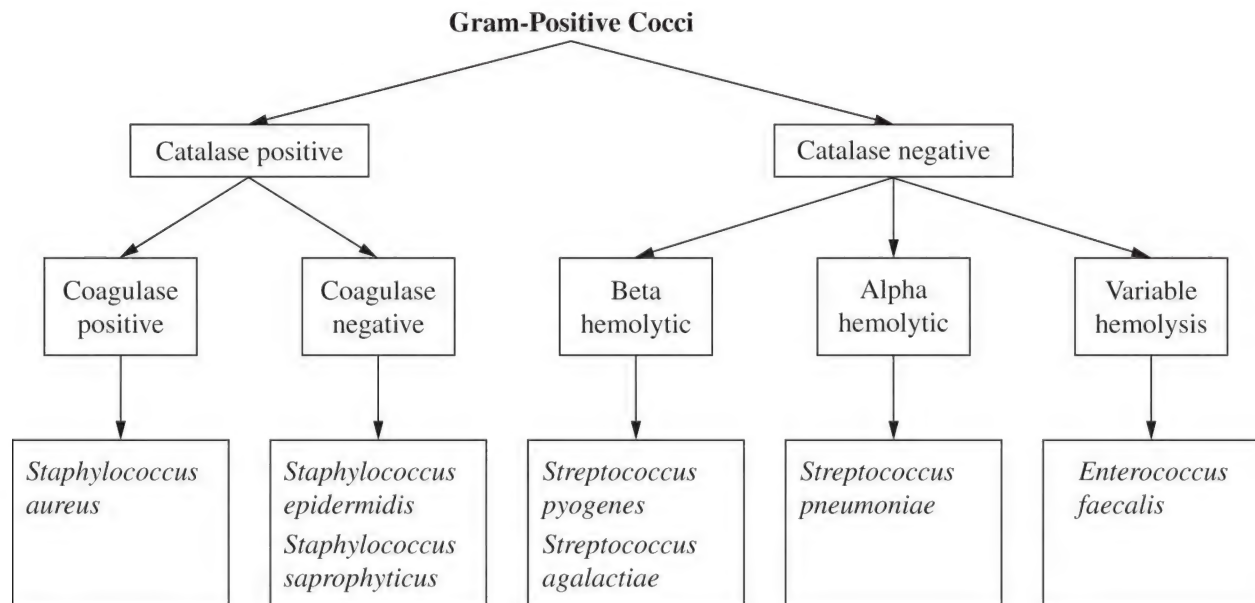
A 70-year old man presents to the Emergency Department with fever, headache, and confusion. His wife reports that he had initially developed respiratory symptoms over a week ago with cough and shortness of breath. The patient is immunosuppressed from recent chemotherapy for hematologic cancer. Upon examination, the patient is lethargic and febrile with a temperature of 38.6°C. Lung exam is notable for crackles in the left lung base, and neurologic exam reveals that the patient is confused and disoriented to time and place. Chest X-ray reveals left lower lobe pneumonia with some nodular lesions. An MRI reveals a brain abscess. Aspiration of the brain abscess is performed. Gram stain of the specimen yields long filamentous, branching chains of gram-positive rods that have a beaded appearance. Modified acid fast staining shows that the organisms are partially acid fast.



Source: Centers for Disease Control and Prevention, Washington, DC

Nocardiosis

Organism and Physical Characteristics:	Nocardiosis is a gram-positive bacterial infection caused by aerobic actinomycetes of the genus <i>Nocardia</i> , which includes over 80 species. The majority of cases are caused by the <i>Nocardia asteroides</i> complex, which is comprised of <i>N. abscessus</i> , <i>N. cyriacigeorgica</i> , <i>N. farcinica</i> , and <i>N. nova</i> . Other known pathogenic species include <i>N. transvalensis</i> complex, <i>N. brasiliensis</i> , and <i>N. pseudobrasiliensis</i> .
Etiology and Epidemiology	<i>Nocardia</i> spp. are found worldwide in soil, decaying vegetable matter, and aquatic environments. The organism can become airborne (eg, associated with dust particles), and inhalation is considered to be a common mode of entry. Other modes of transmission can occur through ingestion or through traumatic cutaneous inoculation. Nocardiosis is considered an opportunistic infection associated with several risk factors such as corticosteroid treatment, immunosuppression, malignancy, organ or hematopoietic stem cell transplantation, HIV/AIDS, and alcoholism.
Clinical Manifestations	<i>Nocardia</i> spp. can cause localized or systemic disease (including cutaneous, lymphocutaneous, pulmonary, and CNS infections). The majority of infections involve the lungs since inhalation is the primary route of bacterial exposure. The organism has a predilection to disseminate to virtually any organ with a particular tropism for the brain.
Pathogenesis	<i>Nocardia</i> spp. cause infection by overcoming host defenses, especially when the host has cell-mediated immune deficiency. The organism appears to have multiple mechanisms for resisting phagocytosis and clearance by host neutrophils and macrophages.
Laboratory Diagnosis	Diagnosis is made by isolation and identification of the organism from a clinical specimen. A Gram stain shows filamentous gram-positive branching rods. On modified acid fast staining, <i>Nocardia</i> spp. are variably, or partially, acid fast due to cell-wall mycolic acid content. Antimicrobial susceptibility testing of the clinical isolate should be performed since there is a high degree of variability among <i>Nocardia</i> spp. PCR can be used for rapid identification of the <i>Nocardia</i> spp.
Treatment and Prevention	Treatment usually involves trimethoprim-sulfamethoxazole as a first-line agent. Combination antimicrobial therapy is recommended for severe infection and may include trimethoprim-sulfamethoxazole in combination with a beta-lactam antibiotic such as a third-generation cephalosporin (eg, ceftriaxone) or a carbapenem (eg, meropenem). Choice of an appropriate and effective antibiotic regimen is essential since the majority of patients with nocardiosis are immunocompromised, infection often involves life-threatening CNS disease, and mortality is high in untreated or inadequately treated infections. There is no vaccine for <i>Nocardia</i> spp.



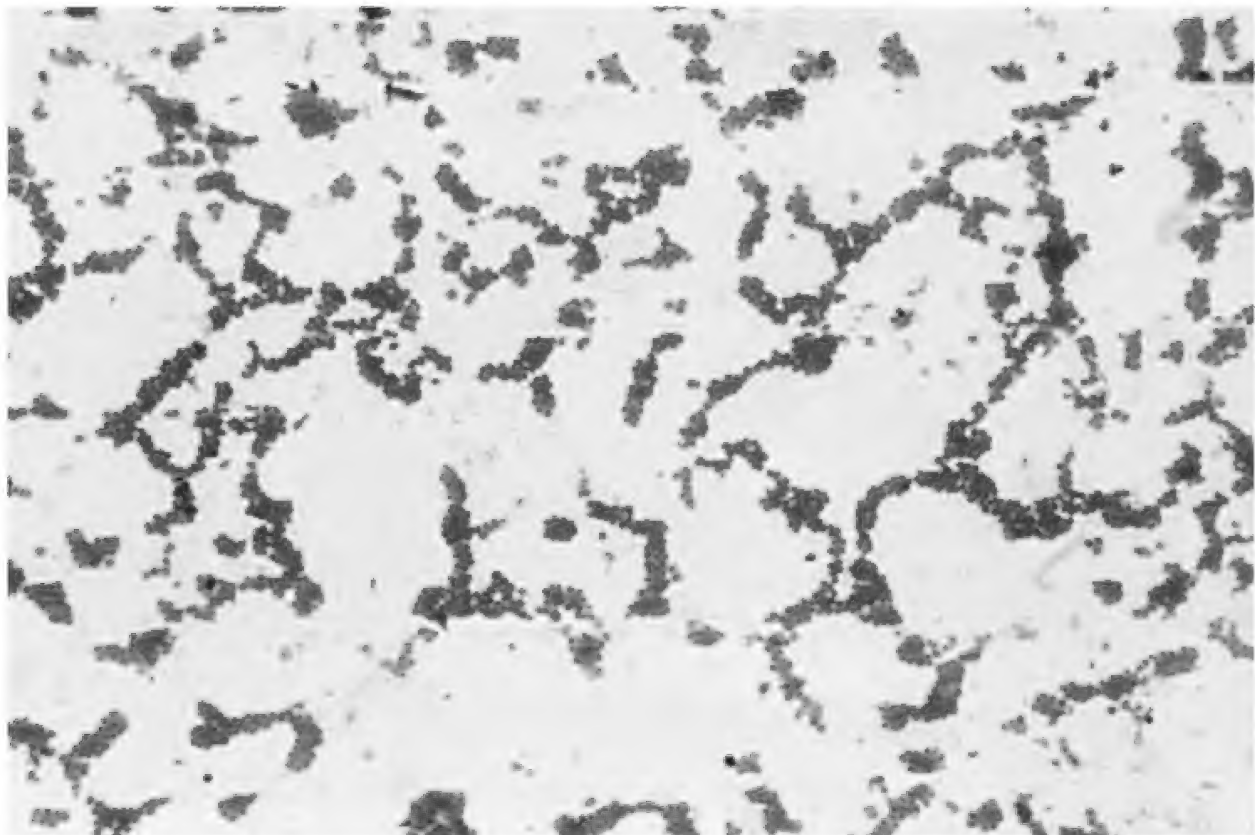
KEY CONCEPTS

- The gram-positive cocci of medical significance encompass three genera: *Staphylococcus*, *Streptococcus*, and *Enterococcus*.

DIFFERENTIAL ATTRIBUTES OF GRAM-POSITIVE COCCI

Organism	Hemolysis	Catalase	Coagulase	Novobiocin Sensitivity	Bacitracin Sensitivity	Optochin Sensitivity
<i>S. aureus</i>	Beta	Positive	Positive	+		
<i>S. epidermidis</i>	Gamma	Positive	Negative	+		
<i>S. saprophyticus</i>	Gamma	Positive	Negative	–		
<i>S. pyogenes</i>	Beta	Negative			+	
<i>S. agalactiae</i>	Beta	Negative			–	
<i>S. pneumonia</i>	Alpha	Negative				+
<i>E. faecalis</i>	Variable	Negative				–
<i>E. faecium</i>	Alpha to Non-hemolytic	Negative				–

About 2 hours after eating warm potato salad at a church picnic, five individuals exhibited abdominal discomfort, nausea, vomiting, and diarrhea. The symptoms resolved after about 18 hours.



Source: Centers for Disease Control and Prevention, Washington, DC.

Food Poisoning

Organism and Differential Characteristics:	<i>Staphylococcus aureus</i> Gram-positive coccus in grape-like clusters, beta hemolytic, catalase positive, coagulase positive.
Etiology and Epidemiology	Normal flora in the anterior nares (10–30%) and vagina (5%). Transmission is by direct contact.
Clinical Manifestations	Food poisoning , by intoxication. Cutaneous infections include Staphylococcal scalded skin syndrome , bullous impetigo , folliculitis , furuncles , styes , and carbuncles . Other manifestations include toxic shock syndrome (TSS) , pneumonia , meningitis , acute endocarditis , osteomyelitis , abscesses in any organ, and septic arthritis .
Pathogenesis	Virulence factors include 22 different heat-stable enterotoxins, cytolytic toxins (alpha, beta, delta, gamma, leukocidins), exfoliative toxins (ETA–heat stable; ETB–heat labile), toxic shock syndrome toxin (TSST1), enzymes (catalase, coagulase, hyaluronidase, lipase, and fibrinolysin), and several structural components including capsules, protein A, and peptidoglycan. The enterotoxins and TSST1 are superantigens .
Laboratory Diagnosis	Staphylococci are catalase-positive , gram-positive cocci that form clusters ; they can grow in the presence of 9% NaCl. <i>S. aureus</i> can be distinguished from other staphylococci by its production of coagulase , its beta hemolysis on blood agar plates, and its ability to ferment mannitol.
Treatment and Prevention	The drug of choice for treating methicillin-susceptible <i>S. aureus</i> (MSSA) is nafcillin. If necessary, alternatives include a first-generation cephalosporin (cefazolin), or in the penicillin allergic patient, vancomycin. Methicillin-resistant <i>S. aureus</i> (MRSA) is increasingly common and is resistant to beta-lactam antibiotics; thus, vancomycin is typically used. Vancomycin-resistant strains are also emerging. An alternative antibiotic is daptomycin but this antibiotic cannot be used for treating pneumonia because it is inactivated by lung surfactant. Prevention involves cleaning wounds properly, washing hands, following good surgical practices, and limiting exposure to patients by health care workers with skin infections.
Notes	

A 47-year-old man complains of tenderness and pain around a peritoneal catheter. The catheter had been placed for dialysis due to chronic renal failure. Blood cultures taken over several days each time reveal gram-positive, catalase-positive, coagulase-negative cocci. The catheter was removed and a course of antibiotics begun.

Catheter Infection

Organism and Differential Characteristics:	<i>Staphylococcus epidermidis</i> Gram-positive coccus in grape-like clusters, catalase positive, coagulase negative.
Etiology and Epidemiology	<i>S. epidermidis</i> is a component of the normal skin flora and is usually transmitted through surgical placement of valves, catheters, and shunts.
Clinical Manifestations	<i>S. epidermidis</i> causes a variety of opportunistic infections including endocarditis associated with prosthetic heart valves and bacteremia associated with infections around intravascular shunts and catheters.
Pathogenesis	<i>S. epidermidis</i> produces a slime layer that adheres to shunts and catheters, allows colonization, and protects organisms from immune clearance.
Laboratory Diagnosis	<i>S. epidermidis</i> is a gram-positive, nonhemolytic coccus. It is catalase positive, coagulase negative, and does not ferment mannitol.
Treatment and Prevention	Many strains of <i>S. epidermidis</i> are resistant to multiple antibiotics including beta-lactam antibiotics, making them difficult to treat. Infections are often treated with vancomycin. Prevention involves removal of intravascular shunts and catheters, good surgical practices, and hand washing.
Notes	

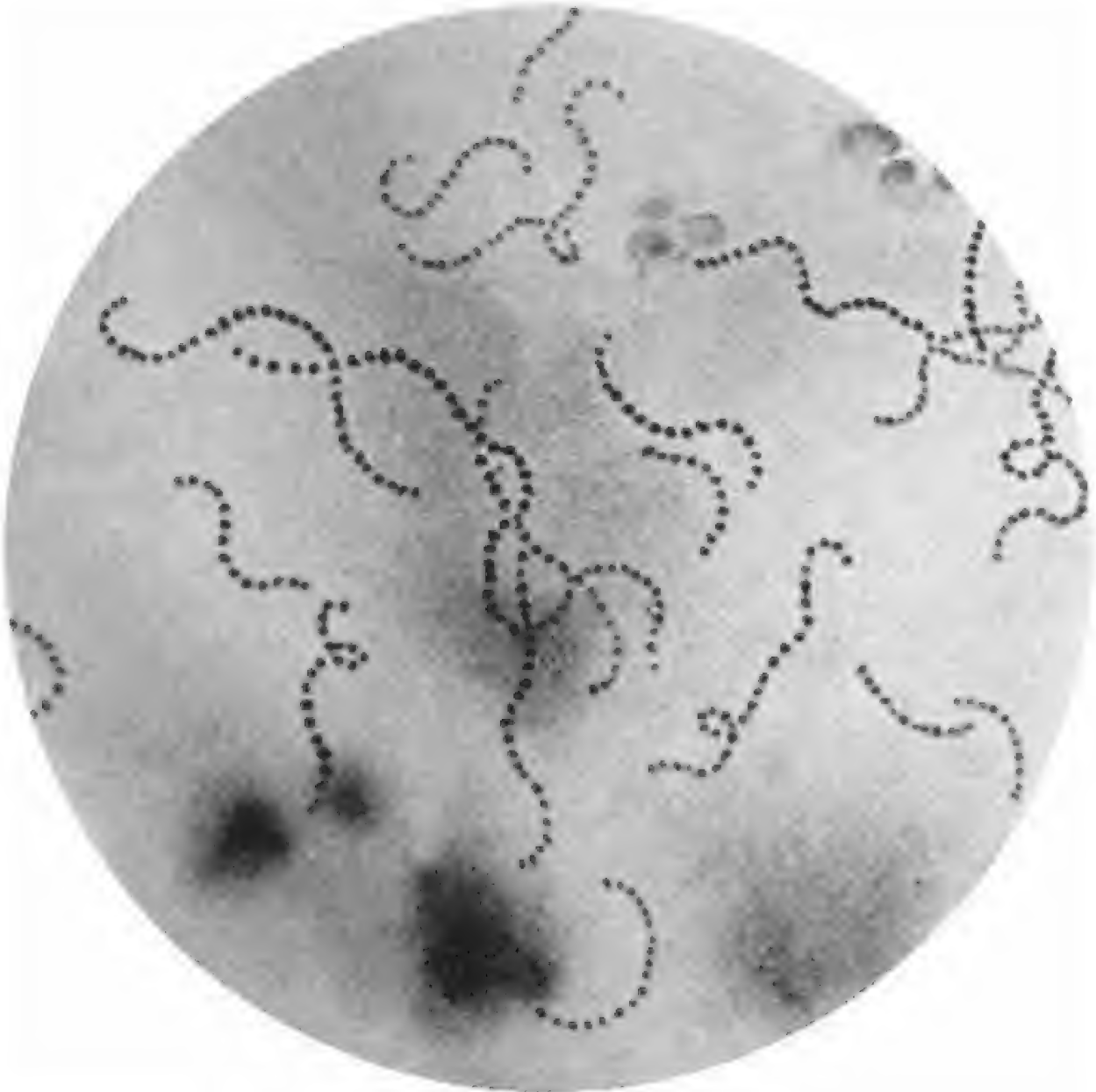
A 17-year-old girl is seen by a physician at the health clinic with complaints of painful urination and urgency. A clean-catch urine sample is sent to the laboratory for testing. History reveals that the patient is sexually active and has had intercourse within the last several days. Culture results a day later reveal 230,000 colonies per mL of a gram-positive, catalase-negative, novobiocin-resistant organism.

Urinary Tract Infection

Organism and Differential Characteristics:	<i>Staphylococcus saprophyticus</i> Gram-positive coccus in grape-like clusters, gamma hemolytic, catalase positive, coagulase negative, novobiocin resistant.
Etiology and Epidemiology	<i>S. saprophyticus</i> is normal flora in the lower urinary tract.
Clinical Manifestations	Common cause of urinary tract infections in sexually active females.
Laboratory Diagnosis	<i>S. saprophyticus</i> is nonhemolytic on blood agar plates. Like other staphylococci, it is catalase positive. Novobiocin resistance sets it apart from other coagulase-negative staphylococci.
Treatment and Prevention	Trimethoprim-sulfamethoxazole is generally effective in treating urinary tract infections due to this organism.
Notes	

A 5-year-old boy wakes up complaining of a sore throat and headache. His mother brings him to the family doctor where examination reveals a fever of

101°F and an erythematous throat. A rapid strep test is performed and results are positive. A throat swab is taken and sent to the laboratory for culture. The child is started on a course of penicillin.



Source: Centers for Disease Control and Prevention, Washington, DC.

Streptococcal Pharyngitis

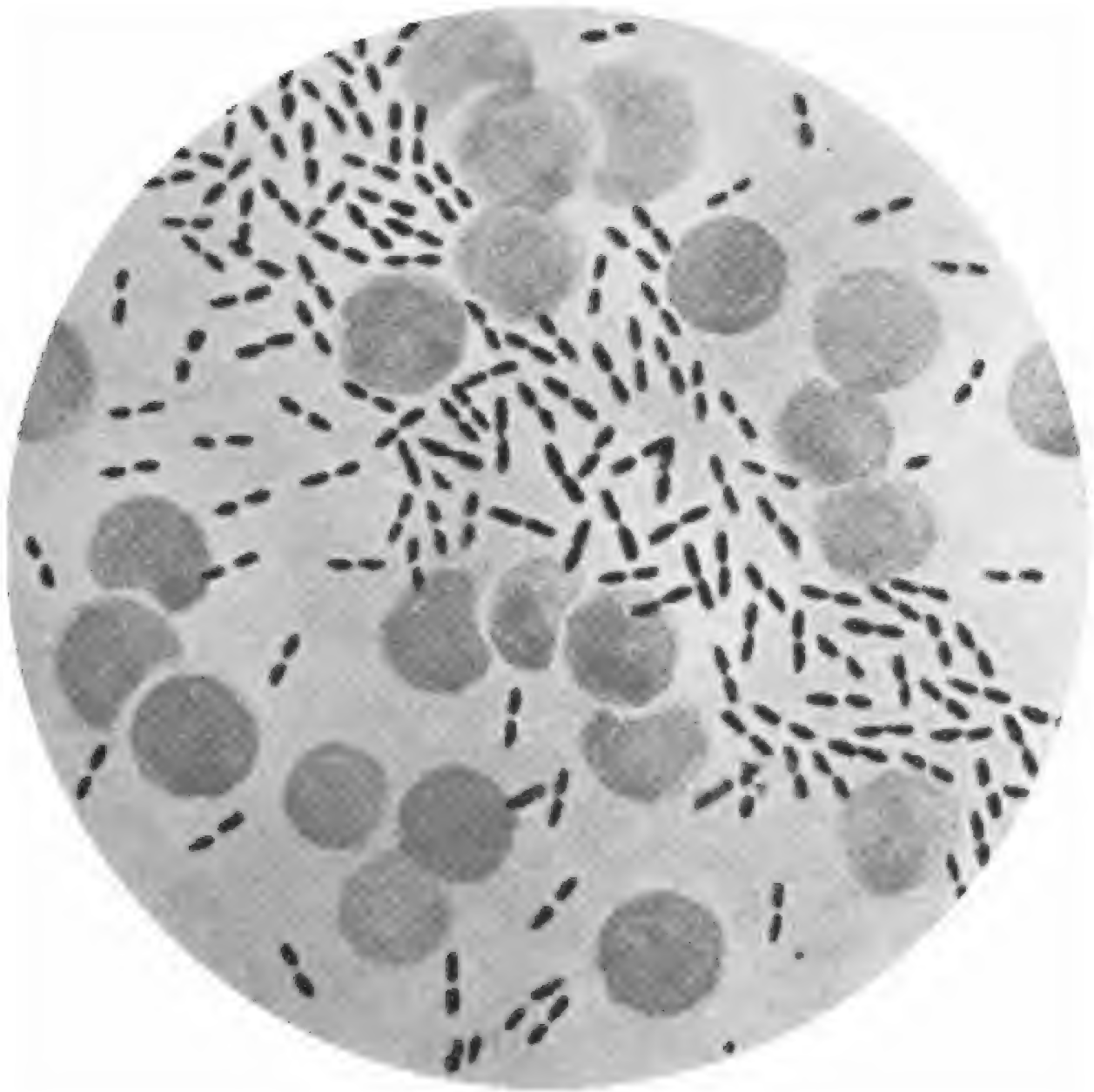
Organism and Differential Characteristics:	<i>Streptococcus pyogenes</i> Gram-positive coccus, chains, Lancefield group A, catalase negative, beta hemolytic, bacitracin sensitive, 80 serotypes based on M protein.
Etiology and Epidemiology	Transmission is by respiratory droplets and direct contact. Skin infections occur through cuts and breaks in skin.
Clinical Manifestations	Pharyngitis is common in children. Scarlet fever is characterized by a diffuse rash, fever, and “strawberry” tongue. Skin and soft-tissue infections include impetigo , erysipelas , and necrotizing fasciitis . Systemic manifestations include streptococcal toxic shock syndrome and sepsis . Rheumatic fever and acute glomerulonephritis are post-infection sequelae.
Pathogenesis	Virulence factors include 3 erythrogenic superantigen toxins (Spe A, B, and C); enzymes (C5a peptidase, hyaluronidase, streptokinase, DNase, streptolysin S, and streptolysin O); and structural components (hyaluronic acid capsule, M protein, F protein, M-like proteins). Rheumatic fever results from M protein autoantibodies that cross-react with heart muscle. Acute glomerulonephritis results from immune complex deposition.
Laboratory Diagnosis	<i>S. pyogenes</i> is catalase negative, beta hemolytic, and sensitive to bacitracin. The rapid strep test is useful for diagnosis of pharyngitis. Negative rapid strep tests are followed by culture. Anti-streptolysin O antibodies (ASOs) are useful for documenting prior <i>S. pyogenes</i> infections in patients with rheumatic fever or acute glomerulonephritis. ASO titers generally rise from pharyngeal but not skin infections.
Treatment and Prevention	<i>S. pyogenes</i> has generally remained susceptible to penicillin and other beta-lactams as well as clindamycin and erythromycin. Deep skin infections may require surgical debridement. Necrotizing fasciitis requires one or multiple surgical debridement(s) in combination with medical treatment; penicillin is the mainstay of antibiotic treatment with addition of clindamycin for the first few days to help reduce the bacterial burden as well as reduce toxin production. Prophylactic antibiotics in individuals with prior rheumatic fever can prevent further heart damage.

A one-week-old infant showing signs and symptoms of pneumonia and meningitis is brought to the emergency room for evaluation. Examination of cerebrospinal fluid by direct antigen latex agglutination is positive for group B *Streptococcus*. Combination antibiotic therapy with penicillin G and an aminoglycoside is begun. Culture results 2 days later confirm beta-hemolytic, gram-positive, catalase-negative, bacitracin-resistant cocci.

Meningitis in a Neonate

Organism and Differential Characteristics:	<i>Streptococcus agalactiae</i> Gram-positive coccus in chains, Lancefield group B, beta hemolytic, catalase negative, 11 serotypes based on polysaccharide capsule.
Etiology and Epidemiology	<i>S. agalactiae</i> colonizes the gastrointestinal and genitourinary tracts and is found in 30% of pregnant women. Early-onset neonatal disease occurs after transmission to neonates either in utero or at birth. Late-onset neonatal disease is transmitted person to person after birth.
Clinical Manifestations	<i>S. agalactiae</i> is also known as group B <i>Streptococcus</i> (GBS). It causes both neonatal and adult disease. Neonatal disease is grouped as either early-onset or late-onset disease. Early-onset disease is seen in infants less than 1-week old and includes pneumonia , meningitis , and sepsis with high mortality and neurologic sequelae. Late-onset disease occurs in infants 1 week to 3 months of age and presents as bacteremia and meningitis . Adult disease includes UTIs in pregnant women; and bacteremia, pneumonia, and skin, joint, and soft-tissue infections in immunocompromised individuals.
Pathogenesis	The antiphagocytic polysaccharide capsule is important for colonization. Neonates lack specific antibodies needed for opsonization. Pathogenesis results from the host inflammatory response.
Laboratory Diagnosis	Culture of blood or CSF will reveal beta-hemolytic, catalase-negative, bacitracin-resistant, gram-positive cocci. Latex agglutination and other antibody-based assays are available for rapid detection of antigen.
Treatment and Prevention	Treatment with penicillin, a cephalosporin, or vancomycin can be used. Prevention includes screening pregnant women for vaginal colonization in the third trimester and antibiotic prophylaxis in high-risk pregnancy during labor. Risk factors include vaginal colonization, prolonged membrane rupture, and premature birth.

A 65-year-old woman is taken to the emergency room by her daughter. She has had “cold”-like symptoms for the past couple of days. This morning, her temperature spiked to 102°F and she experiences shaking chills, pain in her chest, and a productive cough with bloody sputum. Gram stain evaluation of the sputum reveals the presence of gram-positive lancet-shaped diplococci. A sputum specimen is sent to the laboratory for culture and sensitivity testing and a course of penicillin begun. Preliminary laboratory results reported alpha-hemolytic colonies on blood agar.

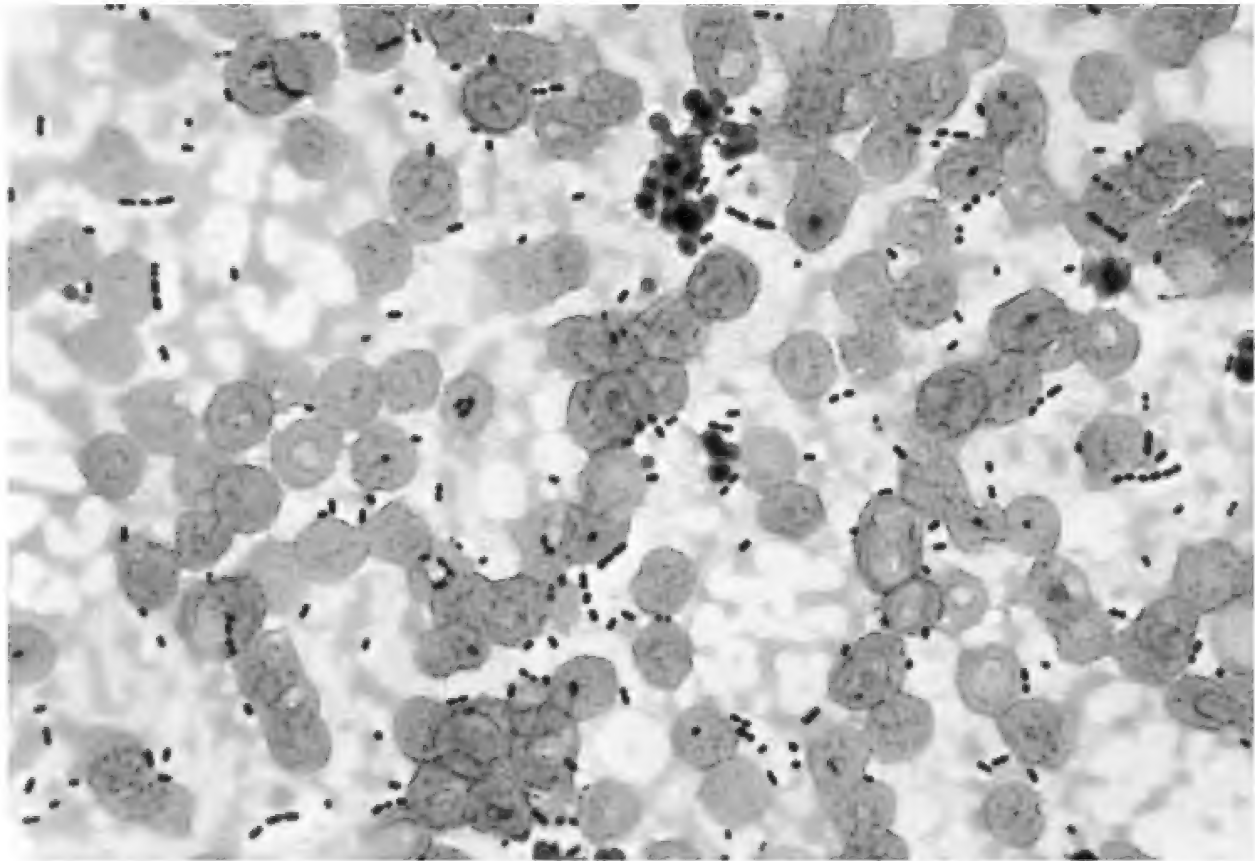


Source: Centers for Disease Control and Prevention, Washington, DC.

Pneumococcal Pneumonia

Organism and Differential Characteristics:	<i>Streptococcus pneumoniae</i> Gram-positive lancet-shaped diplococci, alpha hemolytic, optochin sensitive, over 80 serotypes based on polysaccharide capsule.
Etiology and Epidemiology	Transmission is by direct contact, respiratory droplets, and aspiration of organisms colonizing the oropharynx. Viral respiratory infections and chronic pulmonary diseases increase susceptibility to infection. Meningitis can occur following ear and sinus infections, pneumonia, bacteremia, and head trauma.
Clinical Manifestations	Pneumococcal pneumonia is usually lobar or a diffuse bronchopneumonia, and is characterized by an abrupt onset of fever, shaking chills, and a productive cough. Sputum often contains blood. Bacteremia is common. <i>S. pneumoniae</i> is a common cause of meningitis , otitis media , and sinusitis .
Pathogenesis	Virulence factors include an antiphagocytic polysaccharide capsule , secretory IgA protease , pneumolysin (inhibits phagocytic killing), phosphorylcholine (facilitates invasion), and cell-wall components such as peptidoglycan and teichoic acid that stimulate the host inflammatory response.
Laboratory Diagnosis	Colonies are alpha hemolytic and bile and optochin sensitive. Gram-positive, lancet-shaped diplococci in sputum. Latex agglutination in cerebrospinal fluid. The Quellung reaction is used for type-specific identification.
Treatment and Prevention	Penicillin is drug of choice. Chloramphenicol, vancomycin, and erythromycin have been effective in treating penicillin-resistant strains. A polyvalent polysaccharide vaccine exists for 23 serotypes and recommended for all adults 65 years or older. A pneumococcal conjugate vaccine coupled to a protein carrier protects against 23 serotypes and is available for infants and children and adults 50 years or older.

A 20-year-old woman hospitalized for Crohn's disease experiences pain on urination, frequency, and a low-grade fever. Her urinary catheter is removed and urine sent to the laboratory for culture. Laboratory results reveal greater than 100,000 colony-forming units per mL of gram-positive cocci that are catalase negative and salt tolerant.



Source: Centers for Disease Control and Prevention, Washington, DC.

Urinary Tract Infection Associated with Catheterization

Organism and Differential Characteristics:	<i>Enterococcus faecalis</i> Diseases: Urinary tract infections, endocarditis, intra-abdominal wounds. Gram positive cocci, Lancefield group D, variable hemolysis.
Etiology and Epidemiology	Transmission is usually endogenous or person-to-person fecal-oral. <i>E. faecalis</i> is a normal inhabitant of the GI and GU tracts. Indwelling catheters are sources of urinary tract infections. Blood infections often result from vascular and peritoneal catheters. Prolonged hospitalization with antibiotic therapy can promote a growth advantage.
Clinical Manifestations	Although not particularly virulent, <i>E. faecalis</i> infections are difficult to clear. The two most common disease manifestations are urinary tract infections and bacteremia . Intra-abdominal wounds often contain <i>E. faecalis</i> as a component of mixed infection. <i>E. faecalis</i> -induced endocarditis is associated with previously damaged heart valves.
Pathogenesis	<i>E. faecalis</i> carries resistance to multiple antibiotics , making it difficult to treat. There are no clear virulence factors.
Laboratory Diagnosis	Similar to <i>Streptococcus</i> , <i>Enterococcus</i> species are gram positive and catalase negative. <i>E. faecalis</i> is tolerant to high salt and bile and can hydrolyze esculin.
Treatment and Prevention	<i>E. faecalis</i> is resistant to multiple antibiotics, so treatment usually involves a combination of cell-wall active antibiotics such as ampicillin or vancomycin with an aminoglycoside.

Gram-Negative Cocci



Neisseria gonorrhoeae
Neisseria meningitidis

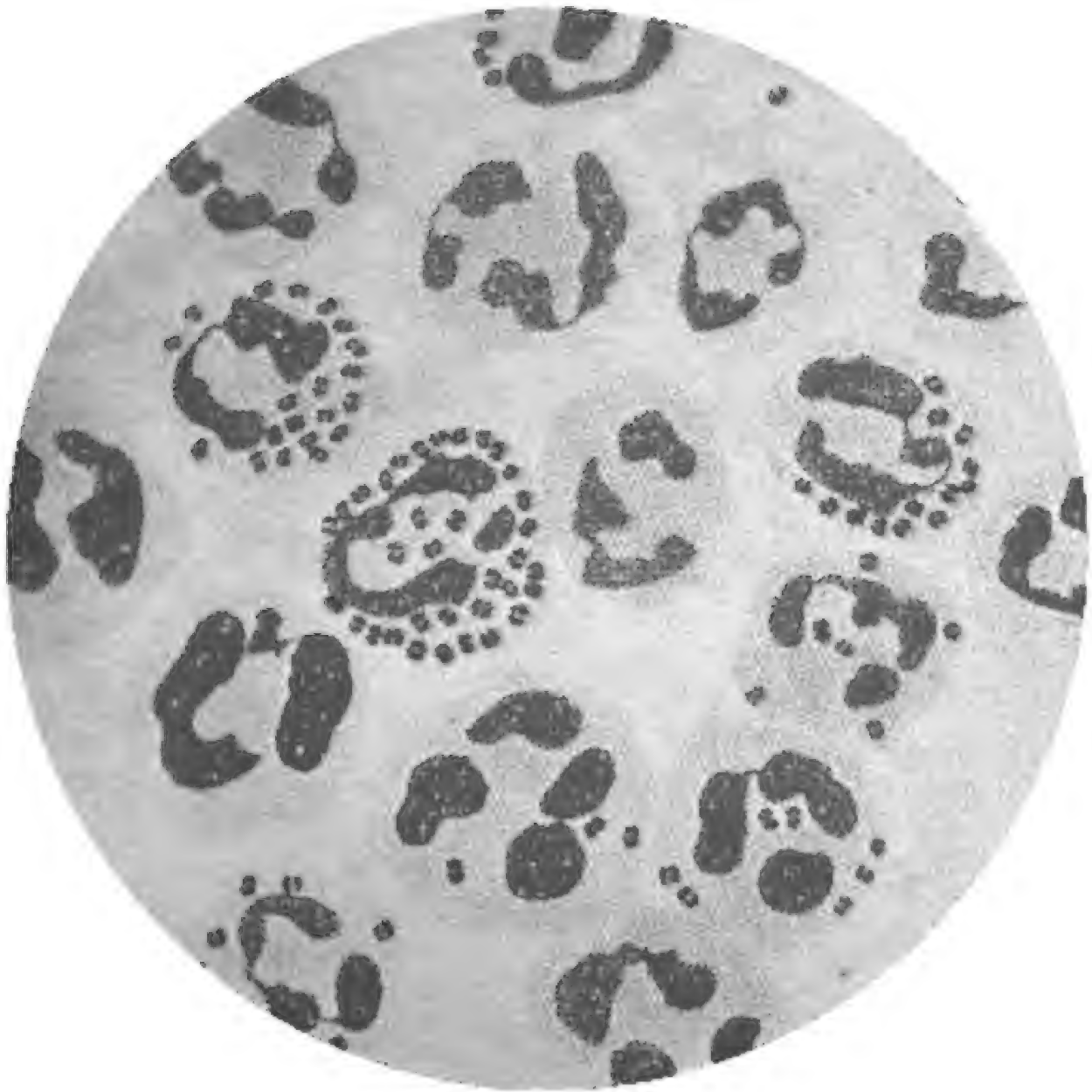
KEY CONCEPTS

- Medically important gram-negative cocci belong to the genus *Neisseria*.
- Typical *Neisseria* are kidney-shaped diplococci.
- Complement plays an important role in immune clearance, so individuals with complement deficiencies are at increased risk of infection.
- The lipopolysaccharide in the cell wall of *Neisseria* is shorter than other gram-negative bacteria and is called lipooligosaccharide or LOS.
- LOS is a potent endotoxin.

PHYSICAL PROPERTIES OF MEDICALLY IMPORTANT GRAM-NEGATIVE COCCI

Organism	Shape	Interesting Properties
<i>Neisseria gonorrhoeae</i>	Kidney-shaped <i>diplococcus</i>	Complex growth requirements Thayer-Martin and chocolate agar media
<i>Neisseria meningitidis</i>	Kidney-shaped <i>diplococcus</i>	Grows on blood or chocolate agar

An 18-year-old male is seen at a health clinic with complaints of painful burning during urination and a milky discharge. Examination of the purulent discharge reveals many neutrophils with intracellular gram-negative diplococci. The patient is treated with a single dose of ceftriaxone, provided with doxycycline to be taken orally twice a day for 7 days, and sent home.

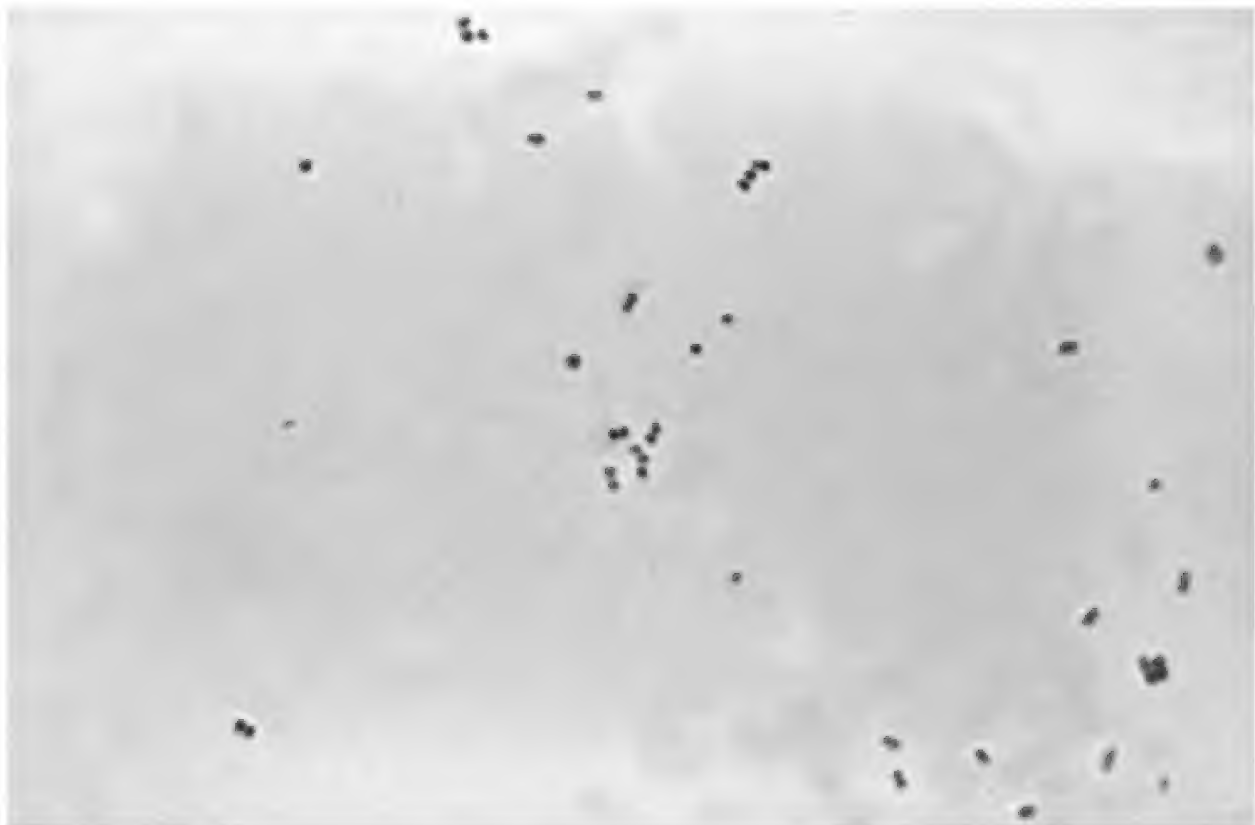


Source: Centers for Disease Control and Prevention, Washington, DC.

Gonococcal Urethritis in a Sexually Active Teenager

Organism and Physical Characteristics:	<i>Neisseria gonorrhoeae</i> Gram-negative diplococcus .
Etiology and Epidemiology	Transmission requires intimate contact such as sexual intercourse or vaginal delivery with newborns. There are no animal reservoirs.
Clinical Manifestations	Major manifestations include urethritis , cervicitis , proctitis , and pharyngitis . Infection can be symptomatic or asymptomatic in sexually active individuals. Extension from the cervix can cause pelvic inflammatory disease . Dissemination can cause sepsis , skin and joint manifestations , and arthritis .
Pathogenesis	Virulence factors facilitate survival and invasion. Pilin and opa proteins are involved in attachment and invasion. Cell-wall lipooligosaccharide is an endotoxin. Antigenic and phase variation allow escape from the humoral immune response. Por protein assists in intracellular survival. Complement is important in immune clearance. Individuals with complement deficiencies are at increased risk for more severe disease.
Laboratory Diagnosis	In men, urethral infections can be diagnosed by the presence of intracellular gram-negative diplococci in a direct Gram stain of a purulent discharge. In women, a positive Gram stain of the cervical discharge must be confirmed by culture. Organisms are usually cultured on Thayer-Martin (a selective medium) or chocolate agar. Nucleic acid amplification tests are widely used for diagnosis.
Treatment and Prevention	Gonorrhea treatment is complicated by the ability of <i>N. gonorrhoeae</i> to develop resistance to antibiotics. In general, penicillin is no longer used but dual therapy with a third-generation cephalosporin (ceftriaxone) and azithromycin remains effective. Persons infected with <i>N. gonorrhoeae</i> are frequently infected with <i>Chlamydia trachomatis</i> , which can be effectively treated with azithromycin or doxycycline. Silver nitrate eye drops are used to prevent gonococcal eye infections in newborns (ophthalmia neonatorum). It is important that the patient's sexual partner(s) also be treated.

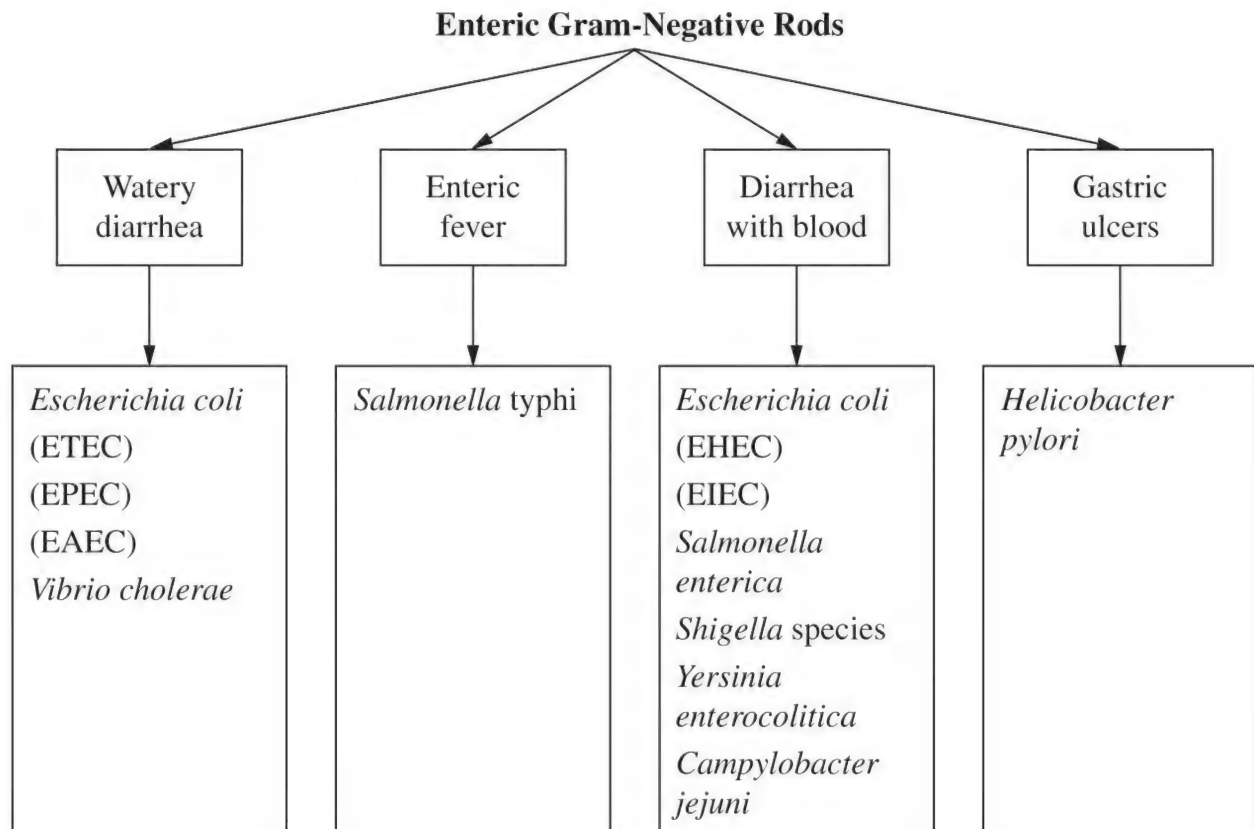
An 18-year-old girl is brought to the college emergency room by her roommate. The roommate claimed that the patient had been feeling fine the night before but this morning had a high fever and was difficult to arouse. On physical examination, the patient was found to have a temperature of 102°F, to be very lethargic with nuchal rigidity, and to have a petechial rash. Examination of her cerebrospinal fluid revealed numerous neutrophils and gram-negative diplococci. Her records indicated that she had received the tetravalent meningitis vaccine before graduating from high school.



Source: Centers for Disease Control and Prevention, Washington, DC.

Meningococcal Meningitis

Organism and Physical Characteristics:	<i>Neisseria meningitidis</i> Gram-negative diplococcus, 13 serogroups based on polysaccharide capsule composition of which A, B, C, Y, W135 are the most important.
Etiology and Epidemiology	<i>N. meningitidis</i> is a human disease. The major mode of transmission is by respiratory droplets from carriers. Outbreaks can arise when carriers and susceptible individuals are brought together under crowded conditions such as university dormitories and military barracks.
Clinical Manifestations	Nasopharynx is the portal of entry. From nasopharynx, organisms may reach bloodstream (meningococcemia). Meningitis is the most common complication of meningococcemia. Widespread petechiae and ecchymoses are signs of meningococcemia . Severe cases can lead to disseminated intravascular coagulation (DIC).
Pathogenesis	Major virulence factors: an antiphagocytic polysaccharide capsule , endotoxin (lipooligosaccharide), IgA₁ protease , and pili . As with <i>N. gonorrhoeae</i> , complement is important in immune clearance through the classical pathway. Individuals with complement deficiencies are at higher risk for dissemination.
Laboratory Diagnosis	Latex agglutination tests are used to diagnose <i>N. meningitidis</i> in cerebrospinal fluid as are direct Gram stains. <i>N. meningitidis</i> can be grown on blood or chocolate agar.
Treatment and Prevention	In general, penicillin or third-generation cephalosporins are effective for treatment. A tetravalent vaccine against serogroups A, C, Y, and W135 is available. The B serogroup polysaccharide (sialic acid) is a poor immunogen and is therefore not in the current vaccine. A high percentage of cases involve serogroup B. A serogroup B vaccine has recently been approved by the FDA. Chemoprophylaxis with rifampin is used for high-risk individuals who have been in close contact with an index case.



KEY CONCEPTS

- Gram-negative rods are the largest group of bacterial human pathogens. They encompass both enteric and non-enteric organisms.

Organism	Virulence Mechanism	Organism	Virulence Mechanism
ETEC	Heat-labile toxin Heat-stable toxin	<i>Salmonella enterica</i>	Endotoxin and invasion
EHEC	Shiga-like toxin	<i>Salmonella typhi</i>	Endotoxin and Vi capsule
EIEC	Plasmid-mediated invasion	<i>Shigella species</i>	Invasion and Shiga toxin
EPEC	Attachment and effacement	<i>Yersinia enterocolitica</i>	Invasion, endotoxin, and heat-stable enterotoxin
EAEC	Plasmid-mediated aggregation and biofilm to block absorption	<i>Campylobacter jejuni</i>	Invasion and enterotoxin
<i>Vibrio cholerae</i>	Heat-labile toxin (cholera toxin)	<i>Helicobacter pylori</i>	Cytotoxin and urease

A newlywed couple on their 5-day honeymoon in Cancun had an unexpected disruption in their vacation. One day after arriving, the groom exhibited abdominal cramping, nausea, and watery diarrhea that kept him in the hotel room for much of the next 4 days. In relating this episode to friends after their return, it is revealed that the groom had ignored warnings about using ice in his beverages.

Traveler's Diarrhea

Organism and Physical Characteristics:	Enterotoxigenic <i>Escherichia coli</i> (ETEC) Gram-negative rod, ferments lactose.
Etiology and Epidemiology	Transmission is by ingestion of contaminated food or water. ETEC is a common cause of traveler's diarrhea.
Clinical Manifestations	Watery diarrhea is the main clinical manifestation.
Pathogenesis	ETEC secretes two different toxins, heat-labile and heat-stable enterotoxin. The bacteria adhere to intestinal epithelial cells but do not invade. Heat-labile toxin is an A-B toxin similar to cholera toxin. It ADP-ribosylates a regulatory G protein, causing a constitutive activation of host adenylate cyclase and elevation of cAMP. The heat-stable toxin targets host guanylate cyclase, resulting in elevation of cGMP.
Laboratory Diagnosis	Many <i>E coli</i> ferment lactose and sorbitol and can be grown on a variety of selective and differential media. Toxin genes can be detected by polymerase chain reaction and/or hybridization. Strain identification is based on serotype analysis of O, H, and K antigens. Whole genome sequencing is of increasing importance for strain identification.
Treatment and Prevention	Watery diarrhea is generally self-limiting and treated with fluid replacement. Diarrheal disease is best prevented by avoiding improperly cooked foods and contaminated water.
Notes	

A 6-year-old girl became ill 24 hours after eating an undercooked hamburger at a local fast food restaurant. Her symptoms began with abdominal cramping

and watery diarrhea and then progressed to bloody diarrhea. Her condition lasted about a week and then resolved. Stool culture grew sorbitol-negative colonies and serotype analysis revealed the presence of *E coli* O157:H7.



Source: Centers for Disease Control and Prevention, Washington, DC.

Hemorrhagic Colitis

Organism and Physical Characteristics:	Enterohemorrhagic <i>Escherichia coli</i> (EHEC) Gram-negative rod, <i>E. coli</i> serotype O157:H7.
Etiology and Epidemiology	Transmission is through ingestion of contaminated food and water. Outbreaks have occurred from a wide variety of sources including undercooked hamburger, unpasteurized apple juice, and contaminated water in swimming pools and water parks. EHEC infections require a very small infectious dose that can be as low as 10 to 100 organisms.
Clinical Manifestations	EHEC causes hemorrhagic colitis and can progress to hemolytic uremic syndrome (HUS) .
Pathogenesis	The major virulence factor of EHEC is a Shiga-like toxin carried by a lysogenic bacteriophage. The Shiga toxin targets and cleaves 28S RNA, resulting in an inhibition of protein synthesis and cell death. EHEC adhere to colonic epithelial cells and secrete toxin that is absorbed by the host cell. Destruction of glomerular endothelial cells results in acute kidney failure and HUS.
Laboratory Diagnosis	EHEC can be differentiated from other <i>E. coli</i> by its inability to ferment sorbitol . Toxin genes can be detected by polymerase chain reaction and/or hybridization. Serotype identification is based on O and H antigens.
Treatment and Prevention	Infections are treated with supportive measures and antibiotics are generally not used. Antibiotics have not been shown to alter the disease course and may increase the risk for development of HUS. Prevention involves proper food handling and hand hygiene.

Notes

A 2-week-old, bottle-fed infant living in a rural area of Southern Mexico exhibits a prolonged course of watery diarrhea. The infant becomes severely dehydrated and dies. It is suspected that the infant formula was prepared using contaminated water.

Infant Diarrhea

Organism and Physical Characteristics:	Enteropathogenic (EPEC) and Enteroaggregative (EAEC) <i>Escherichia coli</i> Gram-negative rods.
Etiology and Epidemiology	EPEC and EAEC are associated with infant diarrhea, especially in developing countries.
Clinical Manifestations	Watery diarrhea often accompanied by vomiting.
Pathogenesis	EPEC attachment to enterocytes of the small intestine stimulates a host cell actin rearrangement, resulting in pedestal formation, destruction of microvilli, and decreased fluid absorption referred to as attachment and effacement pathogenesis. EAEC possesses adherence factors that result in large aggregates and a mucus biofilm that blocks absorption by enterocytes of the small intestine, causing persistent watery diarrhea.
Treatment and Prevention	Fluid replacement is important to prevent dehydration. Diarrheal disease is best prevented by avoiding improperly cooked food and contaminated water.

Notes

One day after enjoying the dinner last night on a cruise ship returning from the Pacific Coast of Mexico, a 60-year-old man exhibits abdominal cramping, diarrhea, fever, chills, and malaise. The diarrhea contains blood and mucus. A

stool sample is sent to the laboratory for analysis. Preliminary results from the laboratory report only lactose-fermenting colonies from the stool.

Bacillary Dysentery

Organism and Physical Characteristics:	Enteroinvasive <i>Escherichia coli</i> (EIEC) Gram-negative rod.
Etiology and Epidemiology	Rare in the United States, most often associated with disease in developing countries.
Clinical Manifestations	Dysentery.
Pathogenesis	EIEC attaches and invades colonic epithelial cells, resulting in cell death and inflammation. Disease process very similar to that of <i>Shigella</i> .
Treatment and Prevention	Disease is self-limiting. Disease is best prevented by avoiding improperly cooked food and contaminated water.
Notes	

Two days after eating undercooked chicken, a 30-year-old fast food manager starts to exhibit abdominal pain, cramping, diarrhea, and nausea. He goes to his family doctor, where a stool sample is collected and sent to the laboratory for analysis and culture. Microscopic examination reveals fecal leukocytes. Preliminary culture results identify several lactose nonfermenting colonies consisting of organisms that are motile and produce H₂S. The patient is treated for symptoms without antibiotics.

Acute Enterocolitis

Organism and Physical Characteristics:	<i>Salmonella enterica</i> (formerly <i>Salmonella choleraesuis</i>) Gram-negative rod, lactose nonfermenter.
Etiology and Epidemiology	<i>Salmonella enterica</i> has thousands of different serotypes. Serotypes are common flora in a wide variety of different animals, especially reptiles, poultry, and birds. Raw chicken eggs may harbor <i>S. enterica</i> , initially in the egg white, although most eggs are not infected. Human infection results from contact with infected animals or ingestion of contaminated animal products. Fecal-oral transmission in food handlers is facilitated by the fact that <i>Salmonella</i> can be shed in human stool for weeks after resolution of diarrheal disease. A moderate infectious dose (about 100,000 organisms) is needed to establish disease.
Clinical Manifestations	<i>Salmonella</i> infection generally results in an uncomplicated dysentery microscopically characterized by erythrocytes and leukocytes in stools. Some very virulent strains can invade the bloodstream causing endotoxin-mediated sepsis.
Pathogenesis	<i>Salmonella</i> bind to intestinal M cells, where they mediate endocytosis. Once internalized, the bacteria replicate in the endosomes and eventually penetrate into the subepithelial tissue, stimulating an inflammatory response. Although most strains remain localized, some strains can penetrate further and enter the bloodstream.
Laboratory Diagnosis	<i>Salmonella</i> can be easily isolated from stool cultures on common selective and differential media due to their inability to ferment lactose. H ₂ S production and motility distinguish <i>Salmonella</i> from other lactose nonfermenters such as <i>Shigella</i> .
Treatment and Prevention	Fluid replacement is essential for any diarrheal disease. Antibiotics are generally not used for <i>Salmonella</i> enteritis because it can prolong the carrier state. Prevention involves proper food handling and adequate hand washing.

A 46-year-old woman just returned from a 1-week long vacation in Central America. Two days after her return, she develops headache, fever, abdominal pain, and constipation. Over the next week, her fever increases and the woman becomes increasingly ill. A blood culture is positive for *Salmonella* Typhi. She is started on a course of ceftriaxone. Her fever lasts another 7 days and then gradually improves.

Enteric (Typhoid) Fever

Organism and Physical Characteristics:	<i>Salmonella Typhi</i> (one of seven serovars of <i>S. enterica</i> subspecies <i>enterica</i>) Gram-negative rod.
Etiology and Epidemiology	The only reservoir for <i>S Typhi</i> is humans. Infection occurs after ingestion of contaminated food or water. Individuals can become chronic carriers, shedding bacteria in stool for months to years, therefore serving as endemic reservoirs.
Clinical Manifestations	<i>Salmonella Typhi</i> is the causative agent of Typhoid fever. Disease starts with gastrointestinal symptoms and progresses to systemic disease. Fever can last 3–4 weeks.
Pathogenesis	<i>S Typhi</i> has two major virulence factors: Vi, an antiphagocytic polysaccharide antigen and endotoxin. As with other <i>Salmonella</i> , <i>S Typhi</i> invades intestinal M cells, replicates in endosomes, and is transported to the subepithelial layer. Here they are engulfed by macrophages, survive, and enter the lymphatics and blood. Replication in spleen and liver leads to continuous release of organisms into the bloodstream. The carrier state is characterized by colonization of the gallbladder.
Laboratory Diagnosis	<i>S Typhi</i> can be isolated from blood cultures in the first and second weeks of illness.
Treatment and Prevention	A variety of antibiotics can be used to control the course of infection including ampicillin, a cephalosporin (ceftriaxone), trimethoprim sulfamethoxazole, or a fluoroquinolone (ciprofloxacin). Prevention involves proper sanitation, carriers not handling food and vaccines against the Vi polysaccharide.
Notes	

A 28-year-old dairy farmer presents to the emergency room with a fever of 101°F, abdominal pain, cramps, and diarrhea containing blood. A stool sample is collected and sent to the laboratory for examination and culture. Preliminary results from the laboratory reveal the presence of lactose nonfermenting organisms that are H₂S negative and nonmotile.

Bacillary Dysentery

Organism and Physical Characteristics:	<i>Shigella</i> Gram-negative rod, four species: <i>S dysenteriae</i> , <i>S flexneri</i> , <i>S boydii</i> , and <i>S sonnei</i> .
Etiology and Epidemiology	Transmission is most often by fecal-oral spread. Ingestion of low numbers of organisms (100–200) can result in infection.
Clinical Manifestations	<i>Shigella</i> causes dysentery that is clinically similar to that caused by enteroinvasive <i>E coli</i> (EIEC). Symptoms include fever, abdominal cramps, and blood and mucus in diarrheal stools. <i>S dysenteriae</i> also produces Shiga toxin, which is associated with more serious disease and development of hemolytic uremic syndrome (HUS).
Pathogenesis	<i>Shigella</i> carries a number of virulence factors including genes required for invasion, endotoxin, and Shiga toxin. As with <i>Salmonella</i> , <i>Shigella</i> invades through intestinal M cells. It then escapes the endosomes, replicates in the cytoplasm, and spreads laterally to adjacent enterocytes. Cell destruction induces a host inflammatory response. Shiga toxin is not required for dysentery. Shiga toxin cleaves 28S RNA, resulting in endothelial cell death in a manner identical to that of enterohemorrhagic <i>E coli</i> .
Laboratory Diagnosis	Like <i>Salmonella</i> , <i>Shigella</i> is lactose nonfermenting and can be isolated on a variety of selective and differential media from stool cultures. Unlike <i>Salmonella</i> , <i>Shigella</i> does not produce H ₂ S and is nonmotile.
Treatment and Prevention	Fluid and electrolyte replacement is often adequate for mild cases, whereas antibiotics such as a cephalosporin (ceftriaxone), fluoroquinolone (ciprofloxacin) or trimethoprim-sulfamethoxazole can be used for more serious disease. Prevention involves proper sanitation and good personal hygiene.
Notes	

A 30-year-old Swedish immigrant living in Minnesota is seen by her family physician with complaints of a swollen and painful left knee. History revealed that she had experienced a case of food poisoning and dysentery 6 weeks prior. The doctor referred the woman to a local rheumatologist, who took a fluid sample from the affected knee. The fluid sample was culture negative. HLA testing revealed the woman had the HLA B27 haplotype.

Reactive Arthritis Following a GI Infection

Organism and Physical Characteristics:	<i>Yersinia enterocolitica</i> Gram-negative rod.
Etiology and Epidemiology	Transmission is through ingestion of contaminated food (eg, insufficiently cooked pork) water, or milk. Infections are most common in colder areas of North America and in Scandinavian countries. <i>Y enterocolitica</i> exhibits increased metabolic activity and growth at refrigerator temperatures, which plays an important role in food-borne transmission.
Clinical Manifestations	Dysentery symptoms are similar to those caused by <i>Salmonella</i> . In immunosuppressed individuals, <i>Y enterocolitica</i> can disseminate from gut to liver and spleen forming abscesses. Reactive polyarthritis is an important sequela most common in individuals with the HLA B27 haplotype.
Pathogenesis	Production of a heat-stable enterotoxin. Replicates in terminal ileum and invades Peyer's patches. Dissemination to regional lymph nodes.
Treatment and Prevention	Fluid replacement is essential as with any diarrheal disease. Serious disease can be treated with antibiotics such as tetracycline in combination with an aminoglycoside (gentamicin). Disease is best prevented by avoiding improperly cooked food and contaminated milk and water.
Notes	

One day after returning from a business trip to South America, a 33-year-old woman abruptly experiences vomiting and watery diarrhea. The diarrhea is frequent and voluminous. The stool is colorless, odorless, and has flecks of mucus in it. She goes to the emergency room where she is started on IV fluids.



Source: Centers for Disease Control and Prevention, Washington, DC.

Severe Watery Diarrhea

Organism and Physical Characteristics:	<i>Vibrio cholerae</i> Slightly curved gram-negative rod, motile.
Etiology and Epidemiology	Transmission is through ingestion of contaminated food or water and by fecal-oral spread. Endemic areas include Africa, Asia, South and Central America, and the Gulf Coast of the United States. Two strains, O1 and O139, are pandemic strains causing serious disease. Many other strains cause mild disease. Shellfish can act as a reservoir for infection. A large inoculating dose (over a billion organisms) is required to induce infection.
Clinical Manifestations	Massive watery diarrhea with flecks of mucus (rice water stools) resulting in rapid dehydration.
Pathogenesis	<i>V. cholerae</i> has four primary virulence factors including cholera toxin, mucinase, flagellum, and adhesins. The mucinase and flagella facilitate penetration of the mucus layer that covers intestinal epithelial cells. Adhesins promote tight binding and the cholera toxin causes diarrheal disease. This A-B toxin is similar in structure and mechanism to enterotoxigenic <i>E. coli</i> heat-labile toxin. Once internalized, the A subunit ADP-ribosylates a regulatory G protein, resulting in constitutive activation of host adenylate cyclase and elevation of cAMP.
Treatment and Prevention	Fluid and electrolyte replacement is essential to correct severe dehydration and salt depletion. Antibiotics such as tetracycline, ampicillin, chloramphenicol, trimethoprim sulfamethoxazole, or a fluoroquinolone (ciprofloxacin) may shorten the duration of symptoms. Prevention involves food hygiene precautions, proper sanitation, waste disposal, and personal hygiene. A short-lived (<50% effective after 2 years) vaccine is available.

A 30-year-old dairy farmer and his family, all of whom regularly consume raw milk, are simultaneously stricken with a gastrointestinal disease. Each has abdominal pain, fever, and diarrhea. The farmer's diarrhea becomes bloody after several days. The family physician sent stool samples to the laboratory for culture. Preliminary results from the laboratory reported growth of *Campylobacter jejuni*. After about a week, the entire family resolved their symptoms.

Gastroenteritis

Organism and Physical Characteristics:	<i>Campylobacter jejuni</i> Gram-negative helical-shaped rod, motile.
Etiology and Epidemiology	A common cause of bacterial gastroenteritis. Commonly found in animal feces. Animals (especially poultry) serve as reservoirs. Human infection results from ingestion of contaminated food or water. Infective dose as low as 800 organisms.
Clinical Manifestations	<i>C. jejuni</i> causes both watery diarrhea and dysentery within 2–5 days of exposure. Symptoms are generally self-limiting after 1–2 weeks. Immunoreactive sequelae such as Reiter syndrome (a form of reactive arthritis), Guillain-Barré syndrome, and erythema nodosum may occur during convalescence.
Pathogenesis	Watery diarrhea is thought to be caused by an enterotoxin. Dysentery results from cellular invasion and destruction, which is likely mediated by a cytotoxin and the host inflammatory response. Guillain-Barré syndrome (acute idiopathic polyneuritis) is a rare disorder of the peripheral nervous system that can be triggered 2–3 weeks after a febrile illness. 20%–40% of cases of Guillain-Barré syndrome are thought to be triggered by <i>C. jejuni</i> infection. The disease is thought to involve antibody production to core lipopolysaccharide present on <i>Campylobacter</i> that cross-reacts with host gangliosides.
Laboratory Diagnosis	<i>C. jejuni</i> is difficult to grow and requires special growth media and conditions including elevated temperature, reduced oxygen, and increased carbon dioxide. For this reason, <i>C. jejuni</i> infections are often not recognized.
Treatment and Prevention	Fluids to maintain hydration. Maintenance of electrolyte balance. Antibiotics such as erythromycin, azithromycin, tetracycline, or ciprofloxacin can be used in severe infections or with immunocompromised patients. Hand washing after handling raw poultry, washing cutting boards and utensils after contact with raw poultry, and thorough cooking of poultry are critical.

A 49-year-old man with chronic gastritis is tested for *H pylori* infection using an antibody test and the urea breath test. Because both are positive, his doctor prescribes a course of clarithromycin, amoxicillin, bismuth subsalicylate, and omeprazole (proton pump inhibitor). After about 3 to 4 weeks, the patient's symptoms have virtually disappeared.

Peptic Ulcer Disease

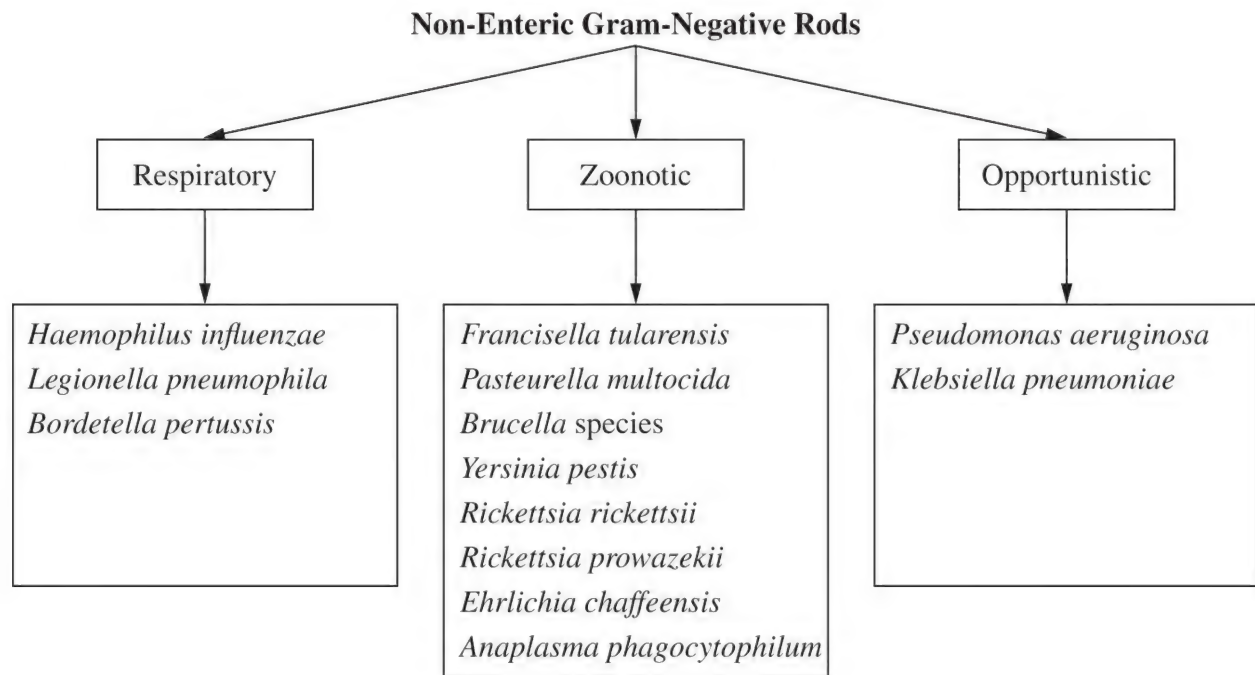
Organism and Physical Characteristics:	<i>Helicobacter pylori</i> Helical-shaped gram-negative rod, motile.
Etiology and Epidemiology	Transmission is not clear but is likely person to person. There are no animal reservoirs.
Clinical Manifestations	Gastritis, gastric and duodenal ulcers, gastric adenocarcinoma.
Pathogenesis	<i>H pylori</i> has several virulence factors including urease, mucinase, polar flagella, adherence factors, endotoxin, and a vacuolating cytotoxin. The urease produces ammonia, resulting in an alkaline microenvironment in the stomach. Mucinase and the flagella allow migration of <i>H pylori</i> through the thick mucus layer covering the stomach epithelial cells. The vacuolating cytotoxin plays a role in destruction of mucin-producing cells. Lowered mucus production in combination with the host inflammatory response results in areas of ulceration.
Laboratory Diagnosis	Invasive and noninvasive procedures are available for diagnosis. Gastric biopsy is the primary invasive procedure. Noninvasive methods include serologic testing to detect antibody to <i>H pylori</i> , stool antigen test, urine ELISA test, and the urea breath test, which is useful for following effectiveness of treatment.
Treatment and Prevention	Treatment of <i>H pylori</i> -induced gastric ulcers involves combination therapy with antibiotics such as amoxicillin, clarithromycin, and metronidazole in combination with proton pump inhibitors and bismuth.

During a summer trip along the Gulf Coast, a 40-year old man and his 38-year-old wife stopped at a roadside stand where they consumed a quantity of raw oysters. About 24 hours later, after returning home, they experienced an acute onset of watery diarrhea accompanied by severe abdominal cramping, mild chills, and headache. They go to the emergency room where stool samples are collected and sent to the laboratory for examination and culture. Microscopic examination reveals the presence of both leukocytes and erythrocytes. Preliminary results from the laboratory reported growth of a curved, rod-shaped gram-negative bacterium. The couple's symptoms resolved without antibiotic treatment.

Acute Diarrheal Disease Caused by *Vibrio*

parahaemolyticus

Organism and Physical Characteristics:	<i>Vibrio parahaemolyticus</i> Slightly curved gram-negative rod, motile and halophilic.
Etiology and Epidemiology	<i>V parahaemolyticus</i> is ubiquitous in coastal waters. Ingestion of raw or inadequately cooked seafood. High infectious dose required. No secondary transmission and no carrier state identified.
Clinical Manifestations	Acute onset of explosive watery diarrhea often with mild to moderately severe cramping abdominal pain. Onset generally within 24 hours of ingestion of the contaminated seafood. Low grade fever, chills, headache may be present. Disease is self-limited.
Pathogenesis	<i>V parahaemolyticus</i> produces an enterotoxin, which seldom causes major intestinal fluid loss. A type III secretion system is capable of injecting virulence proteins into host cells to disrupt host cell function or cause cell death by apoptosis. However, tissue damage caused by this vibrio generally less extensive than that observed in shigellosis.
Laboratory Diagnosis	Diarrheal fluid is characteristically watery, sometimes mucoid. Microscopic examination is not of major diagnostic value. In the majority of cases, few leukocytes and erythrocytes are observed; in some people large numbers of these cell types are seen. Stool culture on TCBS agar and biochemical tests provides definitive diagnosis.
Treatment and Prevention	No treatment required in majority of patients. Antimicrobial therapy shortens neither the clinical course nor the duration of pathogen excretion. Proper cooking of seafood and refrigeration are preventative measures.

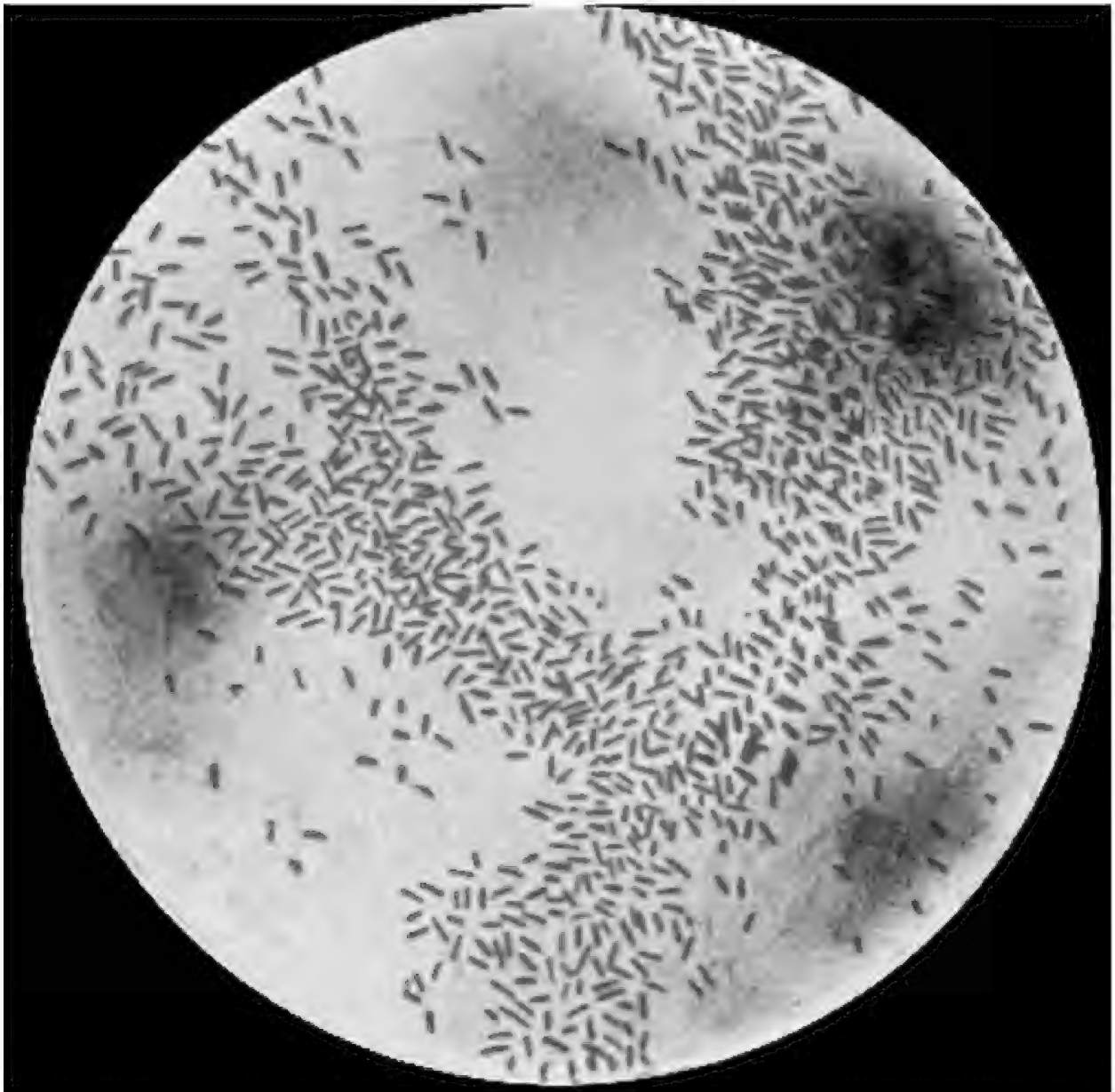


KEY CONCEPTS

SUMMARY OF SYNDROMES CAUSED BY NON-ENTERIC GRAM-NEGATIVE RODS

Organism	Clinical Syndrome	Organism	Clinical Syndrome
<i>Haemophilus influenzae</i>	Pneumonia, otitis media, sinusitis, meningitis	<i>Yersinia pestis</i>	Bubonic plague Pneumonic plague
<i>Bordetella pertussis</i>	Whooping cough	<i>Francisella tularensis</i>	Tularemia—many forms depending on route of entry (ulceroglandular, glandular, oculoglandular, pharyngeal, typhoidal, or pneumonic)
<i>Klebsiella pneumoniae</i>	Pneumonia, urinary tract infections, bloodstream infections	<i>Brucella species</i>	Brucellosis, which can affect any organ system
<i>Pseudomonas aeruginosa</i>	Pneumonia, wound and burn infections, external otitis or swimmers ear, malignant otitis externa, urinary tract infections	<i>Rickettsia prowazekii</i>	Epidemic typhus
<i>Legionella pneumophila</i>	Pontiac fever and Legionnaires' disease	<i>Rickettsia rickettsii</i>	Rocky Mountain spotted fever
<i>Pasteurella multocida</i>	Cellulitis, abscesses and soft tissue infection, osteomyelitis, septic arthritis, tenosynovitis	<i>Ehrlichia chaffeensis</i>	Human monocytic ehrlichiosis (HME)
		<i>Anaplasma phagocytophilum</i>	Human granulocytic anaplasmosis (HGA)

An 18-month-old boy is brought to the hospital with a headache, fever, and lethargy. He had a 2-day history of an upper respiratory illness and has no history of vaccination. A lumbar puncture revealed 20,000 white blood cells per mL with 85% polymorphonuclear cells. Gram stain of the cerebrospinal fluid revealed many PMNs and pleomorphic gram-negative rods. A latex particle agglutination test detected the presence of capsular polysaccharide in the CSF.



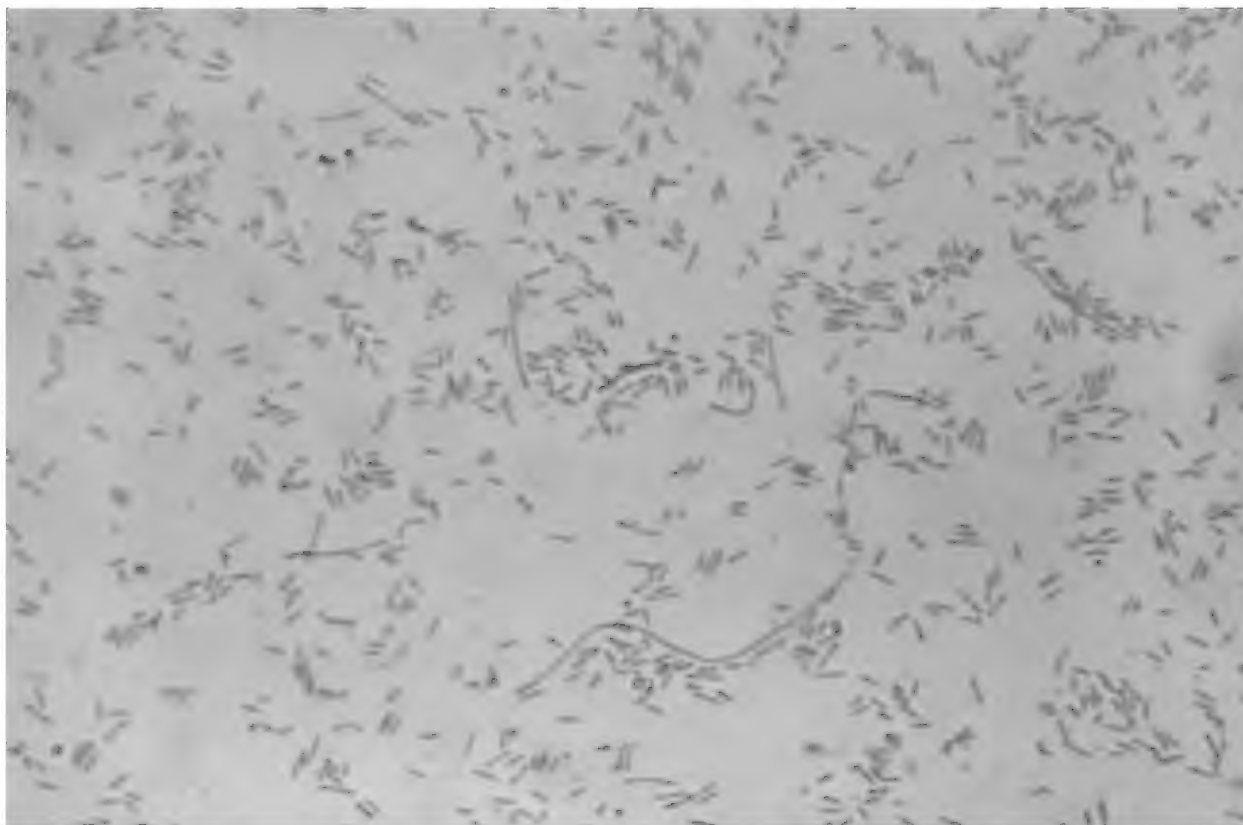
Source: Centers for Disease Control and Prevention, Washington, DC.

Meningitis in a Child

Organism and Physical Characteristics:	<i>Haemophilus influenza</i> Gram-negative coccobacilli, requires X (heme) and V (NAD) factors for growth.
Etiology and Epidemiology	Six serotypes (a–f) of encapsulated strains based on distinct capsular polysaccharide antigens. Unencapsulated (nontypable) strains also exist and are less invasive. Infants and young children are particularly susceptible. Sporadic outbreaks result from direct contact with respiratory secretions containing encapsulated serotypes. Type b (polyribosyl ribitol phosphate capsule) is the most common pathogen.
Clinical Manifestations	Most serious manifestations include either pneumonia or meningitis. <i>H influenzae</i> type b also causes pharyngitis, epiglottitis, sinusitis, otitis media, cellulitis, septic arthritis, and conjunctivitis. Meningitis in young children is associated with a high incidence of neurologic complications that range from hearing loss to severe mental retardation.
Pathogenesis	Virulence factors include the antiphagocytic capsule, endotoxin, IgA protease, and pili. Immune clearance requires protective antibodies to the capsule to facilitate opsonization. The host inflammatory response is the primary pathogenic mechanism.
Laboratory Diagnosis	<i>H influenzae</i> type b antigen can be detected directly in cerebrospinal fluid using a latex particle agglutination test. Culture medium requires X and V factors, which are present in chocolate agar.
Treatment and Prevention	Antibiotic choice requires susceptibility testing and includes an aminopenicillin (ampicillin) if the organism is susceptible, or a third-generation cephalosporin (ceftriaxone or cefotaxime). Rifampin is sometimes used as chemoprophylaxis for exposed family members. Prevention involves vaccination of children under 5 years of age with a conjugated purified type b capsular polysaccharide. No cross-protection to other serotypes.

Notes

A 60-year-old man with a history of smoking is hospitalized with a nonproductive cough and multifocal pneumonia. He had a fever of 40°C and appeared flushed. A minimal amount of sputum was collected and sent to the laboratory for microscopic examination. No organisms could be seen by Gram stain but a direct fluorescent antibody (DFA) stain of a sputum smear was positive.

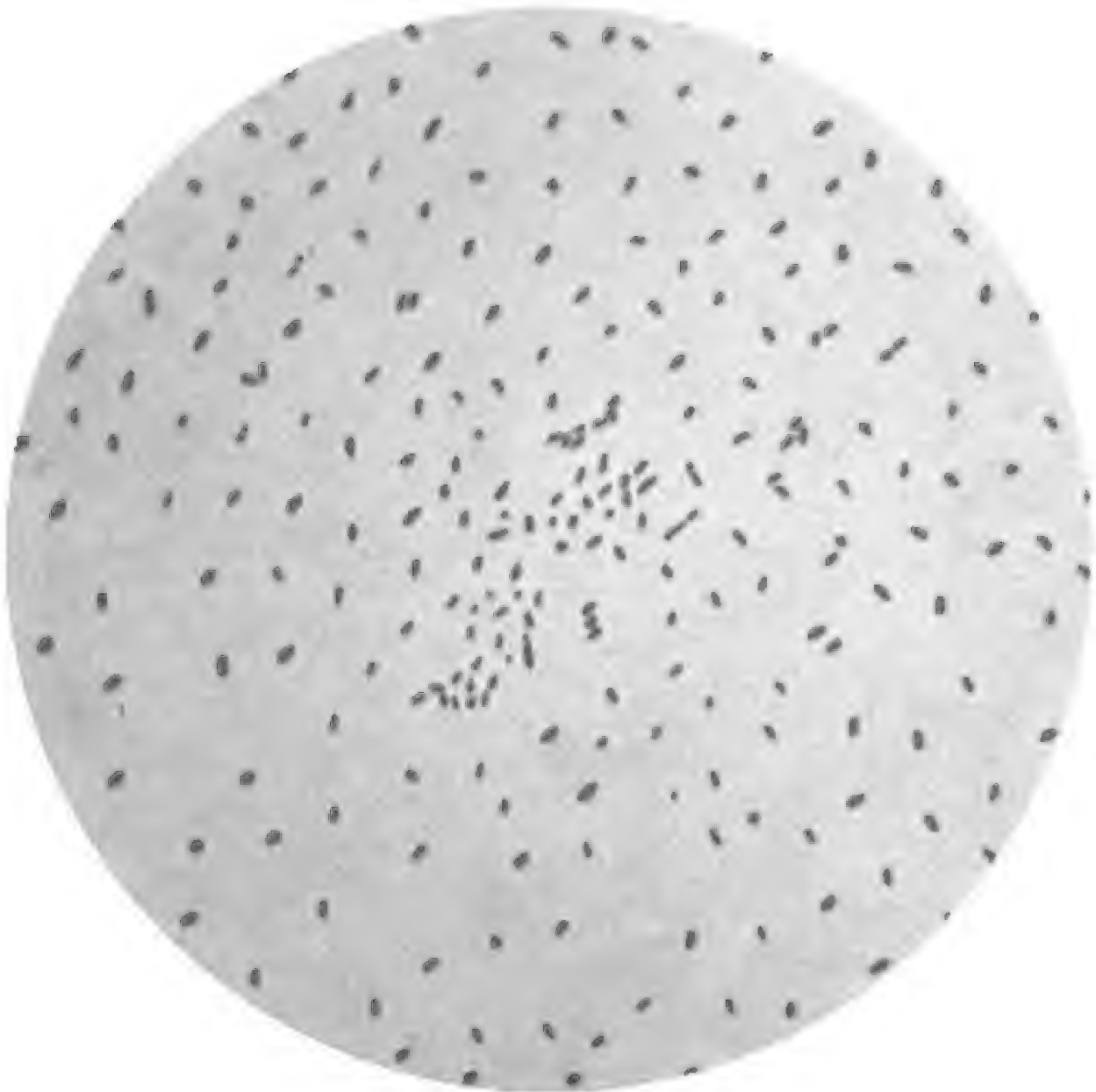


Source: Centers for Disease Control and Prevention, Washington, DC.

Atypical Pneumonia

Organism and Physical Characteristics:	<i>Legionella pneumophila</i> Thin, aerobic, pleomorphic, gram-negative rod.
Etiology and Epidemiology	<i>L. pneumophila</i> is a fastidious aquatic microorganism that is found in water sources such as lakes and streams as well as in air conditioning systems, hot tubs, hospital showers, and devices used for inhalation therapy. <i>L. pneumophila</i> is a facultative intracellular pathogen that can invade and multiply in free-living amoebae where they are protected from the action of chlorination. Transmission is through inhalation of aerosols containing bacteria. Individuals with weakened pulmonary defenses or those who are immunocompromised are most susceptible to infection.
Clinical Manifestations	The two primary forms of disease include Pontiac fever and Legionnaires' disease. Pontiac fever is a mild disease characterized by an "influenza"-type illness. Legionnaires' disease is more severe and characterized by fever, dry cough, and a multifocal necrotizing atypical pneumonia.
Pathogenesis	The major virulence mechanisms involve cell wall endotoxin and the ability to parasitize and survive within alveolar macrophages. Intracellular survival results in decreased immune clearance. Lung damage results from the host inflammatory response.
Laboratory Diagnosis	Special media containing high levels of cysteine and iron are required for growth. Diagnosis involves a variety of methods including antigen detection, serology, direct microscopy with Dieterle silver stain (stain poorly with Gram stain), direct fluorescent antibody, and culture.
Treatment and Prevention	Because many <i>Legionella</i> species carry beta lactamases, penicillins are not very effective. Antibiotics such as the newer macrolides (especially azithromycin) or respiratory tract fluoroquinolones (especially levofloxacin) are preferred agents. These agents are preferred over older macrolides (erythromycin) or tetracyclines (tetracycline) due to their more potent intracellular activity and pharmacokinetic properties. Prevention involves identification of contaminated water sources and measures such as hyperchlorination to reduce bacterial loads.

A 3-year-old immigrant from Mexico is admitted to the hospital with a history of a persistent cough. Upon admission, the boy's cough becomes rapid and prolonged with intervals of high-pitched deep breaths. The peripheral white blood count is 24,000/ μ l, with an absolute lymphocytosis. The child does not have a history of any vaccinations.

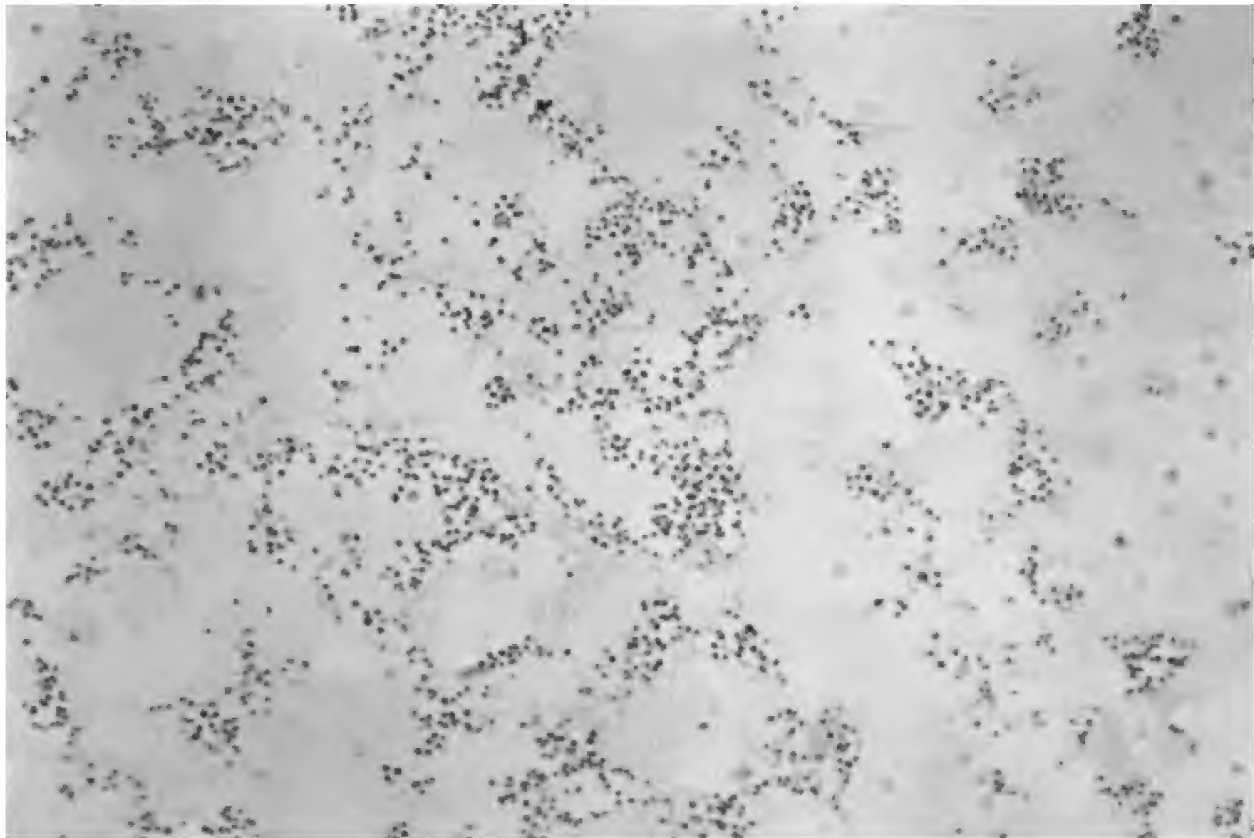


Source: Centers for Disease Control and Prevention, Washington, DC.

Persistent and Severe “Whooping” Cough

Organism and Physical Characteristics:	<i>Bordetella pertussis</i> Small gram-negative coccobacilli. Aerobic.
Etiology and Epidemiology	<i>B pertussis</i> is a highly contagious respiratory pathogen spread by airborne droplets. Humans are the only host.
Clinical Manifestations	Causative agent of whooping cough (“the cough of 100 days”). This three-stage disease is most infectious in the first “cold-like” or catarrhal stage. The second, paroxysmal stage is characterized by paroxysmal coughing, copious mucus production, and exhaustion. During the third, convalescent stage, the cough subsides over a period of several weeks to months.
Pathogenesis	<i>B pertussis</i> carries several virulence factors that work together to cause disease. Attachment to sulfatides on ciliated respiratory epithelial cells is mediated by filamentous hemagglutinin (Fha). Once anchored, tracheal cytotoxin (a peptidoglycan fragment) stops the cilia from beating. Pertussis toxin (Ptx) ADP ribosylates host G proteins in the early stages of respiratory infection. Ptx is an A-B toxin which targets respiratory tract macrophages and promotes lymphocytosis. Adenylate cyclase toxin and Ptx elevate intracellular cAMP levels and increase mucus secretion.
Laboratory Diagnosis	Isolation of <i>B pertussis</i> requires special media.
Treatment and Prevention	Antibiotics such as a macrolide (azithromycin is preferred; alternatively, erythromycin or clarithromycin) or trimethoprim-sulfamethoxazole are effective in reducing the bacterial load. Supportive care including suction of respiratory mucus and supplemental oxygen may also be required. Prevention involves vaccination either with killed organisms or with an acellular vaccine directed against Fha and Ptx. Pertussis vaccine usually administered in combination with toxoids of diphtheria and tetanus (DTP).
Notes	

A 48-year-old Arkansas man is seen by his primary care doctor for an ulcerated lesion on his right index finger. Axillary lymph nodes are enlarged and painful. He has had a fever and headache for the last 24 hours. History reveals that the man is an avid hunter who has killed and dressed several animals including a rabbit and a muskrat within the last week.

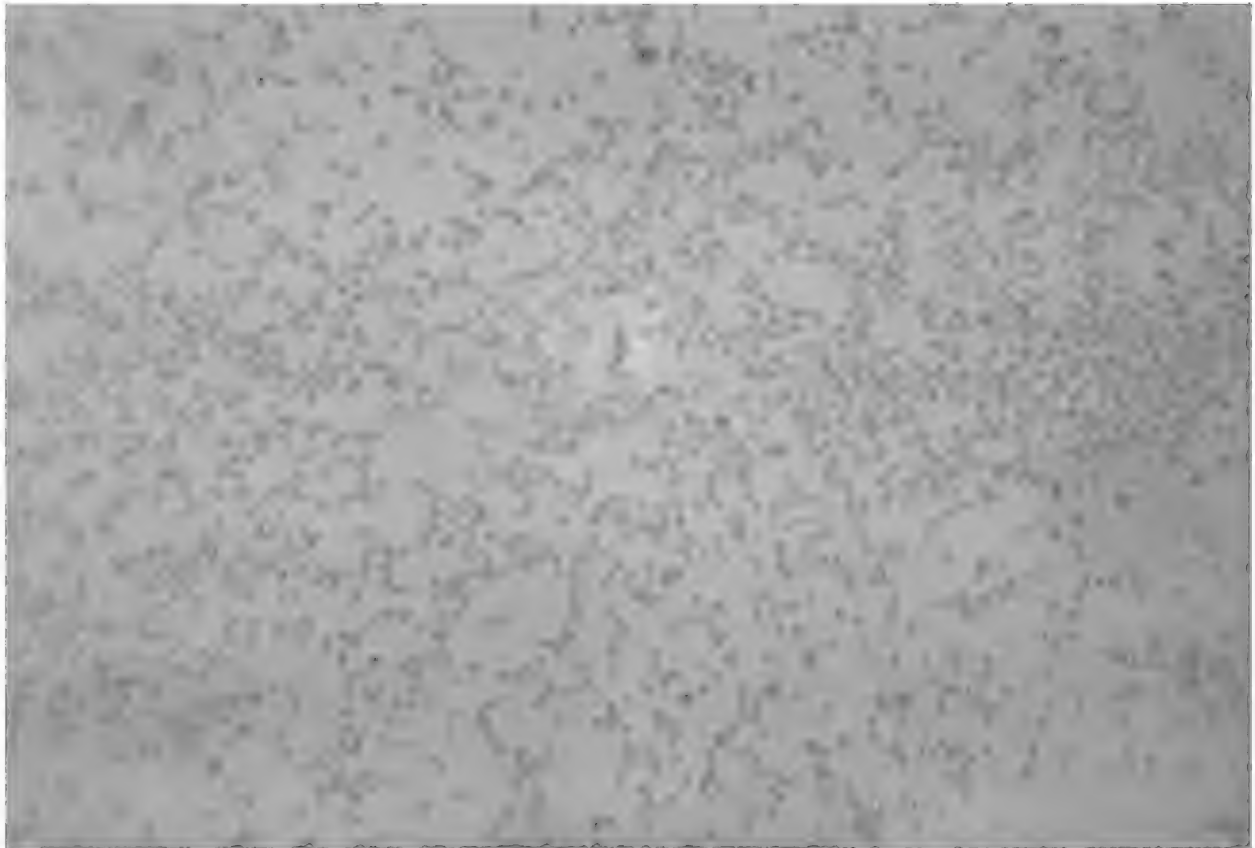


Source: Centers for Disease Control and Prevention, Washington, DC.

Tularemia

Organism and Physical Characteristics:	<i>Francisella tularensis</i> Small gram-negative coccobacillus.
Etiology and Epidemiology	This highly infectious organism is endemic to many areas of the United States including Arkansas, Missouri, and Oklahoma. Infection results from bites from infected ticks, infectious aerosols, and contact with infected tissues or body fluid of an infected animal. The infectious dose is around 50 organisms. Not transmitted human to human.
Clinical Manifestations	A variety of disease manifestations include ulceroglandular disease, oculoglandular conjunctivitis, glandular disease, typhoidal disease, and pneumonia.
Pathogenesis	Two primary virulence factors include an antiphagocytic capsule and endotoxin. A facultative intracellular pathogen, <i>F. tularensis</i> can survive in cells of the reticuloendothelial system. The protein IgIC is required for phagosomal breakout and intracellular replication.
Laboratory Diagnosis	Diagnosis is facilitated using culture, fluorescent antibody assays on clinical specimens, serologic assays to detect specific antibody, or nucleic acid amplification assays. The organism is slow growing and requires special cysteine-rich media. Because it is highly infectious, laboratories should be notified of suspected infections by the clinician.
Treatment and Prevention	<i>F. tularensis</i> is resistant to beta-lactam antibiotics. Antibiotics such as an aminoglycoside (streptomycin or gentamicin), fluoroquinolone (ciprofloxacin), or tetracycline (doxycycline) have been effective in treatment. A vaccine is available for high-risk individuals. Prevention involves avoidance of infected animals, aerosols, and tick vectors.
Notes	

A 7-year-old boy is taken to the family doctor with complaints of a sudden-onset of fever and chills. Physical examination reveals a painful swollen lesion on his right index finger. Questioning reveals the boy was bitten by his sister's cat 1 day prior. After cleaning the cat bite, he is started on a course of penicillin and sent home.

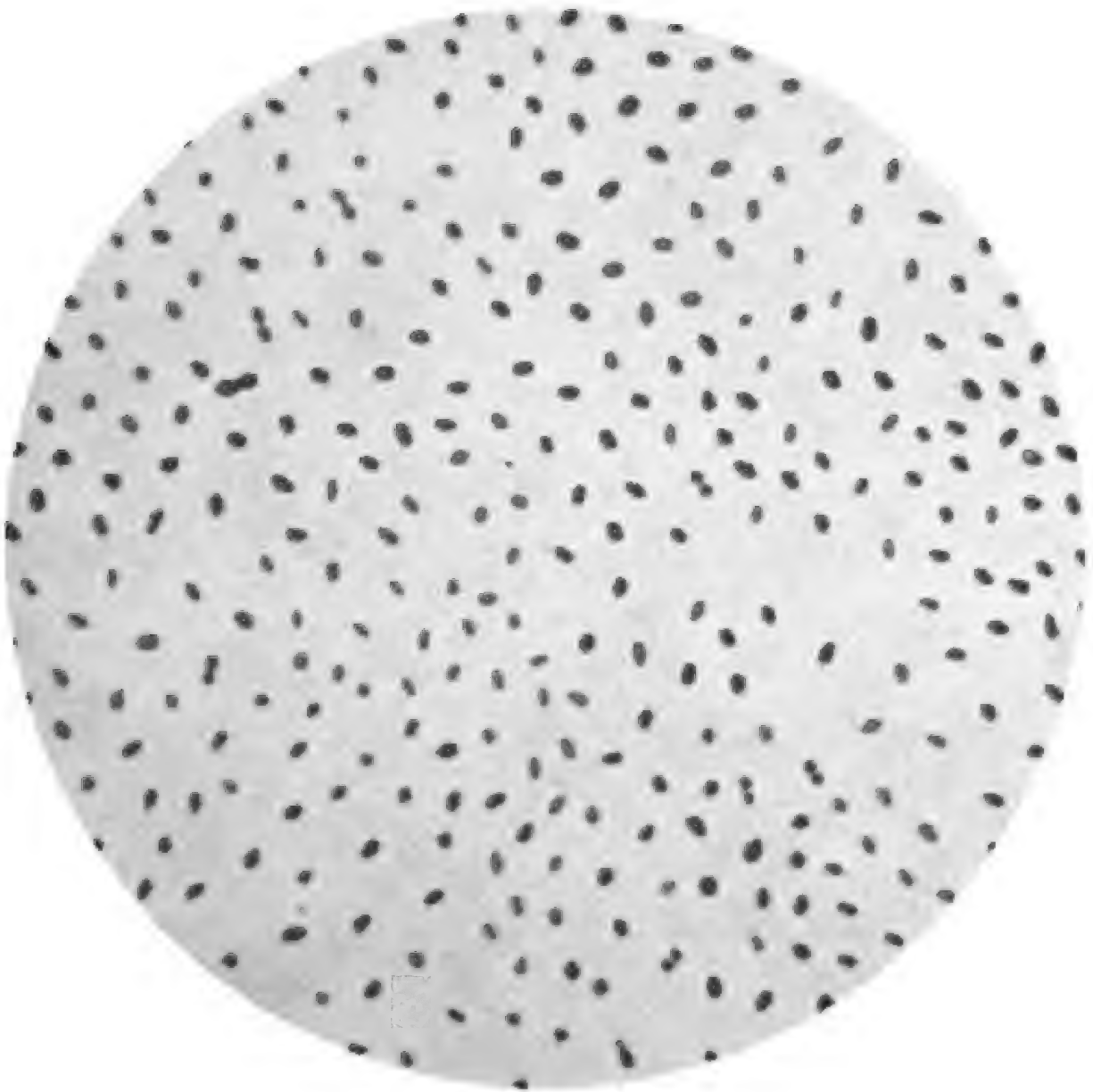


Source: Centers for Disease Control and Prevention, Washington, DC.

Cat Bite Fever

Organism and Physical Characteristics:	<i>Pasteurella multocida</i> Nonmotile, gram-negative coccobacilli with a bipolar appearance on stained smears. Currently classified into five serogroups (A-F) based on capsular polysaccharide antigens.
Etiology and Epidemiology	<i>P. multocida</i> causes a range of diseases in animals and birds. In humans, it is the most common infection associated with a scratch or bite from a cat or dog. It is part of the respiratory flora of animals, and human infection usually occurs through direct inoculation. Respiratory spread from animals to humans also occurs.
Clinical Manifestations	Cellulitis is the most common finding and usually occurs within 24 hours of the scratch or bite. Local complications, such as septic arthritis, osteomyelitis, and tenosynovitis, are common. Less common complications include respiratory tract infection, bacteremia causing an osteomyelitis or endocarditis, and meningitis.
Pathogenesis	<i>P. multocida</i> has several virulence factors including lipooligosaccharide, an antiphagocytic capsule, and hyaluronidase. The primary pathogenic mechanism involves host cell inflammation.
Treatment and Prevention	A variety of antibiotics are generally effective including penicillin or a derivative (ampicillin, amoxicillin-clavulanate), a third generation cephalosporin (ceftriaxone), a tetracycline (doxycycline), or trimethoprim-sulfamethoxazole. Wound drainage or debridement may be necessary. Prevention involves avoidance and proper cleansing of animal bites.
Notes	

A 30-year-old woman seeks medical help after several weeks of fatigue and weight loss. During this time, she had also experienced a fever and headache with sweats and chills that cleared and then returned. History reveals that she regularly drinks unpasteurized goat milk. The physician suspects *Brucella* infection and sends a blood sample to the laboratory for culture and serologic testing. In the meantime, he prescribes a 6-week course of tetracycline and rifampin while awaiting results.

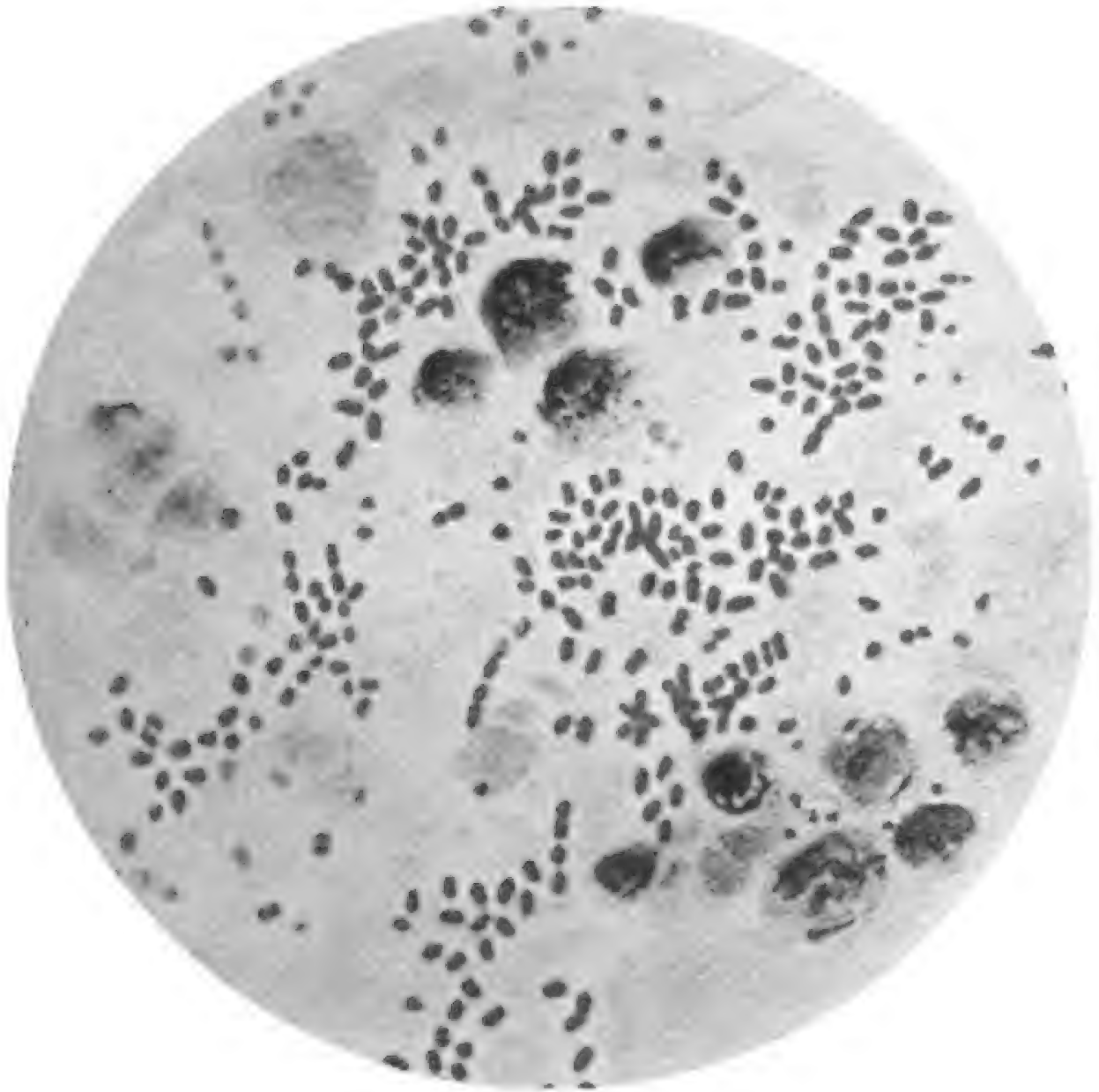


Source: Centers for Disease Control and Prevention, Washington, DC.

Brucellosis

Organism and Physical Characteristics:	<i>Brucella species</i> Small, nonmotile, gram-negative, facultative intracellular coccobacillus. Four important biovars: <i>B melitensis</i> , <i>B abortus</i> , <i>B suis</i> , and <i>B canis</i> .
Etiology and Epidemiology	A zoonotic disease of wild and domestic animals. Most human infections result from contact with infected animals either through direct inoculation into cuts and breaks in skin or through ingestion of contaminated milk or cheese. The four biovars have different animal reservoirs: <i>B melitensis</i> (goats and sheep), <i>B abortus</i> (cattle), <i>B suis</i> (swine), and <i>B canis</i> (dogs).
Clinical Manifestations	Brucellosis is commonly known by a variety of names including Malta fever, undulant fever, and Mediterranean remittent fever. Incubation period is 1–6 weeks. Disease is characterized by a slow-onset, periodic or undulating fever with sweats, chills, headache, fatigue, and anorexia. Brucellosis can become chronic or typhoidal lasting for months. Complications may include arthritis, epididymo-orchitis, and endocarditis, resulting in death. The most severe disease is caused by <i>B melitensis</i> and <i>B suis</i> .
Pathogenesis	Intracellular survival in cells of the reticuloendothelial system induces granulomas and periodic release of endotoxin into the circulation, resulting in remittent fevers. Prolonged survival gives rise to chronic or typhoidal disease.
Laboratory Diagnosis	Serology (IgG agglutination test, ELISA), clinical findings, and blood culture are used in diagnosis. Laboratory acquired infections are common.
Treatment and Prevention	Treatment involves a prolonged course of antibiotics (6 weeks or more) such as a tetracycline (doxycycline) in combination with an aminoglycoside (streptomycin or gentamicin), or rifampin. Trimethoprim-sulfamethoxazole is an additional agent that might be added to the regimen in some cases. Prevention involves elimination of infected animals, pasteurization of milk products, and animal vaccination.
Notes	

A 21-year-old woman is seen by her family doctor with complaints of a high fever and a large swollen lump in the groin area. Physical examination reveals a fever of 38.9°C and a large swollen lymph node in the groin. History revealed that she had returned 4 days previously from a camping trip in the Four Corners region of the Southwestern United States. Blood and pus were collected from the lymph node and sent to the laboratory for culture and analysis. The patient was started on a course of streptomycin.

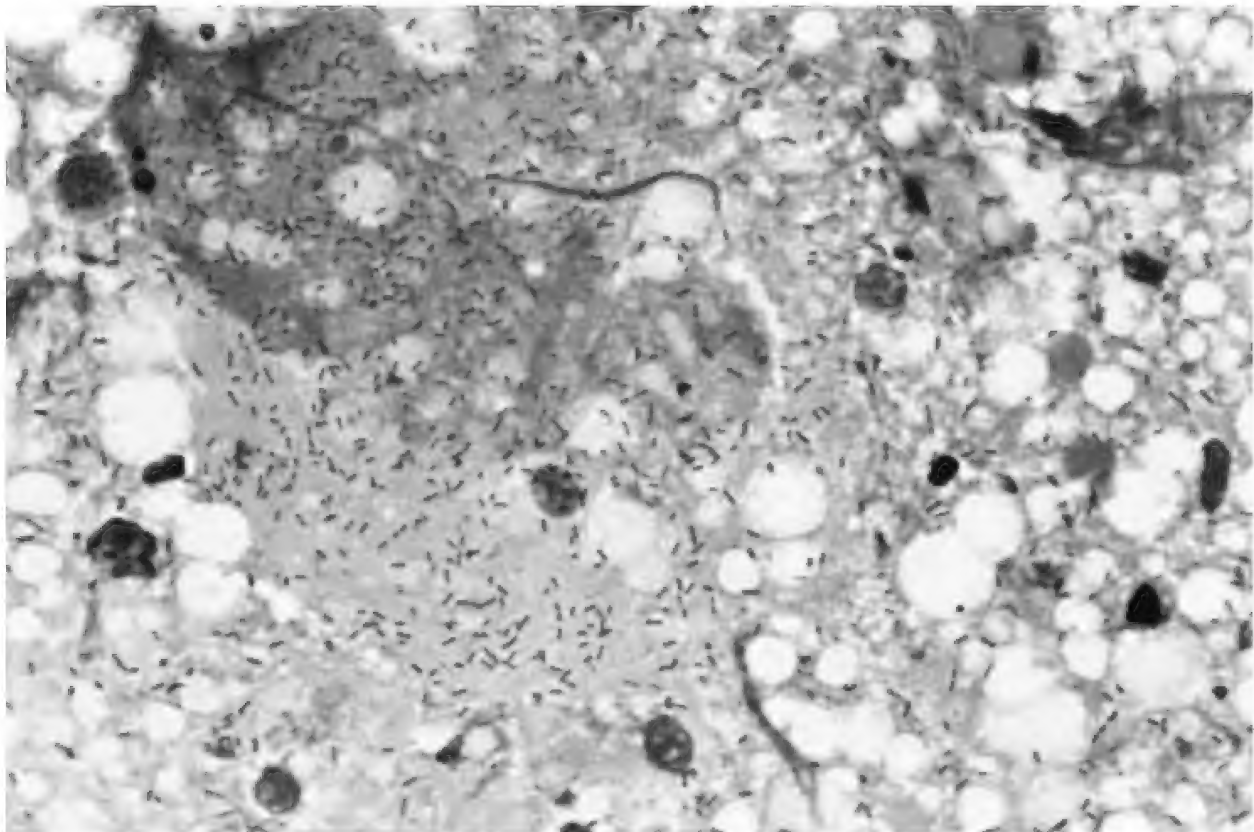


Source: Centers for Disease Control and Prevention, Washington, DC.

Plague

Organism and Physical Characteristics:	<i>Yersinia pestis</i> Nonmotile gram-negative rod that exhibits bipolar staining with special stains.
Etiology and Epidemiology	Transmission is either through bites of infected fleas from wild animals (sylvatic plague) or rats (urban plague) or person to person through respiratory aerosols. Endemic areas in the United States focus around the western states (AZ, NM, CO, CA).
Clinical Manifestations	Three major forms: Bubonic plague is characterized by high fever and large swollen inguinal, axillary, or cervical lymph nodes called bubos . Progression can result in a bacteremic phase with sudden onset of fever and chills. Pneumonic plague results from inhalation of infectious aerosols or dissemination of bacteremic organisms to the lung. Disease development is rapid and highly fatal. Septicemic plague results from endotoxin effects including necrosis of peripheral blood vessels and disseminated intravascular coagulation. It is the least common of the three types.
Pathogenesis	Virulence factors include a protein capsule (F1 antigen), V antigen (inhibits neutrophil chemotaxis), endotoxin, plasminogen activator protease, and a series of YOPS proteins that interfere with host cell signaling and disrupt the host cell cytoskeleton. Type III secretion systems responsible for the injection of proteins directly into the cytoplasm of the host cell. Survival and replication inside macrophages facilitate massive inflammatory lymph node swelling. Plasminogen-activating protease facilitates spread in the human while activity of a <i>Yersinia</i> coagulase causes blood ingested by the flea to clot and block the proventriculus where the bacteria proliferate, thus facilitating transmission.
Laboratory Diagnosis	If plague is suspected, the laboratory should be notified. Direct examination after staining and culture from blood, sputum, or bubo aspirate aids in diagnosis.
Treatment and Prevention	The antibiotic of choice is the aminoglycoside, streptomycin. Other aminoglycosides (gentamicin), tetracyclines (doxycycline, tetracycline), fluoroquinolones (ciprofloxacin, levofloxacin, moxifloxacin), or chloramphenicol are alternatives. Drug resistance has been noted in <i>Y. pestis</i> . Prevention involves avoidance of handling dead animals in endemic areas and controlling rat populations in urban areas. No vaccines are currently available.

A 12-year-old is seen by his family doctor with complaints of fever, severe headache, muscle aches, and a petechial rash covering his body. The mother mentions that the rash started on the wrists and ankles and then progressed inward to cover his body. On questioning, it was revealed that the boy had recently returned from a 5-day camping trip in West Virginia. His mother remembers removing several ticks from his legs after he returned home.



Source: Centers for Disease Control and Prevention, Washington, DC.

Rocky Mountain Spotted Fever (RMSF)

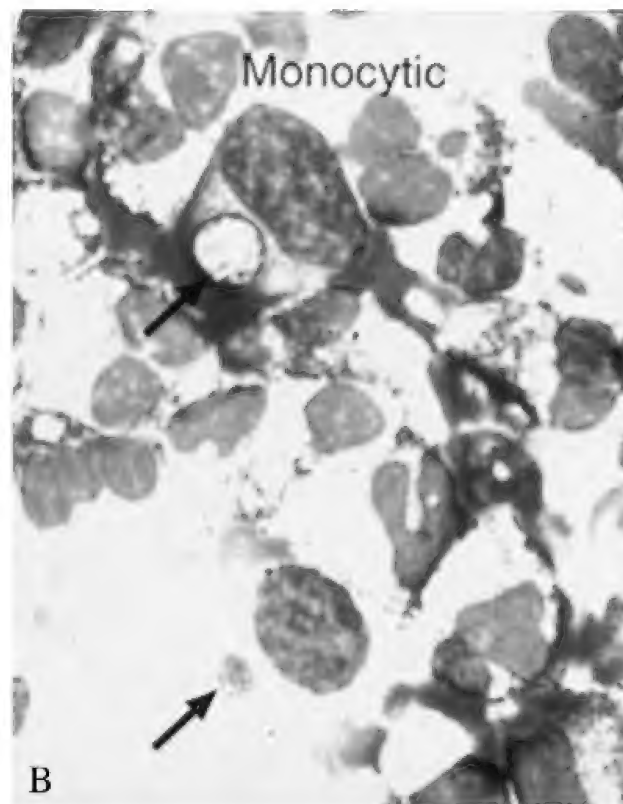
Organism and Physical Characteristics:	<i>Rickettsia rickettsii</i> Obligate intracellular gram-negative coccobacillus
Etiology and Epidemiology	Transmission is through prolonged exposure to infected <i>Ixodidae</i> (hard-bodied) ticks (<i>Dermacentor variabilis</i> , <i>D andersoni</i> , <i>Rhipicephalus sanguineus</i>). The organism is endemic to many areas of the United States, especially the south Atlantic, southeastern, and south central states. Transmission parallels tick season in a given geographic area.
Clinical Manifestations	<i>R rickettsii</i> is the causative agent of RMSF. Symptoms include a characteristic petechial rash , acute fever, headache, chills, and myalgias. The rash typically starts at the extremities (wrists and ankles) and then spreads inward toward the trunk. Systemic complications include encephalitis, renal failure, and disseminated intravascular coagulation (DIC). Without treatment, fatality rates approach 20%–30%.
Pathogenesis	<i>R rickettsii</i> are obligate intracellular parasites that replicate in endothelial cells causing vasculitis and blood vessel damage. Systemic infection causes increased vascular permeability and petechial bleeding, and can lead to DIC.
Laboratory Diagnosis	Diagnosis is based on clinical signs and symptoms of the patient. It can be confirmed by indirect fluorescent antibody, enzyme immunoassay, or immunohistochemical staining of skin biopsy specimens.
Treatment and Prevention	Prompt treatment with antibiotics such as a tetracycline (doxycycline or tetracycline) or chloramphenicol. Sulfonamides enhance the disease and are contraindicated. Prevention involves containing and eliminating the vectors and prompt removal of ticks.

While volunteering with Doctors Without Borders, a young doctor visits a refugee camp where an epidemic has broken out. Many of the sick refugees are experiencing high fevers, severe headaches, chills, and myalgias. Physical examination revealed that most were infested with body lice; some had a maculopapular rash while others had a petechial rash on the trunk and limbs but not on the palms of the hands or soles of the feet.

Epidemic Typhus

Organism and Physical Characteristics:	<i>Rickettsia prowazekii</i> Obligate intracellular gram-negative coccobacillus.
Etiology and Epidemiology	Transmission from person to person is by the body louse (<i>Pediculus humanus subsp humanus</i>). <i>R. prowazekii</i> is excreted in feces when the louse takes a blood meal. Infected feces are rubbed into skin when scratching the bite site. Infection may also occur by mucous membrane inoculation of infected feces.
Clinical Manifestations	<i>R. prowazekii</i> is the causative agent of epidemic typhus. A characteristic petechial rash begins on the trunk and spreads outward to the limbs, usually not affecting the palms of hands and the soles of the feet. Other symptoms include acute onset of fever, chills, and myalgias. Systemic complications include meningoencephalitis. <i>R. prowazekii</i> can establish a latent infection, which can reactivate years later (Brill-Zinsser disease).
Laboratory Diagnosis	Serology (indirect fluorescent antibody, enzyme immunoassay, latex agglutination) is useful for diagnosis.
Treatment and Prevention	Antibiotics such as a tetracycline (doxycycline or tetracycline) or chloramphenicol have been successfully used in treatment. Prevention involves improvement of living conditions and delousing with insecticides.
Notes	

A 40-year-old male presents to the Medicine Clinic with a 2-day history of fevers, chills, headache, nausea, and myalgias. He lives in Tennessee and has been enjoying the current July summer weather with hiking trips and golf lessons. Upon examination, the patient is uncomfortable and ill appearing. He has a fever of 39.6°C. There is no rash, no adenopathy, and no organ enlargement. Clinical laboratory work-up reveals leukopenia, anemia, thrombocytopenia, elevated liver enzymes, and elevated creatinine.



Source: Centers for Disease Control and Prevention, Washington, DC.

Ehrlichiosis and Anaplasmosis

Organism and Physical Characteristics:	<i>Ehrlichia chaffeensis</i> (causes human monocytic ehrlichiosis, HME); <i>Anaplasma phagocytophilum</i> (causes human granulocytic anaplasmosis, HGA). Obligate intracellular gram-negative bacteria that infect human monocytes or granulocytes. Clinical and laboratory findings are similar although these are distinct tick-borne infections.
Etiology and Epidemiology	<p>Transmission is through exposure to infected ticks. The principal vector for <i>E. chaffeensis</i> (HME) is the Lone Star tick (<i>Amblyomma americanum</i>); the principal animal reservoir is the white tail deer. HME is endemic in the southeastern, south central, and mid-Atlantic regions of the United States (it can also occur in New England and the Pacific Northwest, Europe, Africa, and Central America).</p> <p>The principal vector for <i>A. phagocytophilum</i> (HGA) is <i>Ixodes scapularis</i> (which is also the tick that serves as the vector of Lyme disease and babesiosis in eastern/northeastern United States), <i>I. pacificus</i> (in western United States), or <i>I. ricinus</i> (in Europe), and the principal animal reservoirs are deer and the white-footed mouse. HGA usually occurs in the upper Midwest, East Coast, and West Coast of the United States, and in Europe. Transmission parallels the presence of the vector and animal reservoirs during tick season.</p>
Clinical Manifestations	Incubation period can range from 1-2 weeks after a tick bite. Symptoms are generally nonspecific and include fever, chills, nausea, vomiting, headache, and myalgias. <i>E. chaffeensis</i> (HME) is more likely to cause severe disease than <i>A. phagocytophilum</i> (HGA). Complications of HME may include meningoencephalitis, seizures, coma, renal failure, respiratory failure, myocarditis, and shock. Clinical laboratory findings may reveal leukopenia, thrombocytopenia, anemia, elevated creatinine, elevated liver enzymes.
Pathogenesis	<i>E. chaffeensis</i> and <i>A. phagocytophilum</i> are obligate intracellular bacteria that infect circulating leukocytes, erythrocytes, and platelets where they multiply within phagocytic vacuoles. Clusters of replicating ehrlichiae can appear in host cells as morulae (derived from the Latin word for "mulberry" due to the appearance of the intracellular bacterial clusters).
Laboratory Diagnosis	HME and HGA can be confirmed serologically using the indirect fluorescent antibody (IFA) test, or by PCR assay. Microscopic examination of leukocytes in peripheral blood may reveal morulae in granulocytes in approximately 20%–80% of HGA patients and in mononuclear cells in approximately 1%–20% of HME patients.
Treatment and Prevention	Infection is typically treated with a tetracycline, with doxycycline being the preferred agent. Prevention involves containing and eliminating the vectors and prompt removal of ticks.

A 66-year-old woman with chronic lung disease is admitted to the intensive care unit of a hospital and placed on a respirator. She subsequently develops a fever and cough with purulent sputum. Chest X-rays reveal a diffuse bilateral bronchopneumonia. A sputum Gram stain reveals numerous leukocytes and gram-negative rods. Culture of the sputum reveals colonies with a fruity aroma.

An Opportunistic Pneumonia

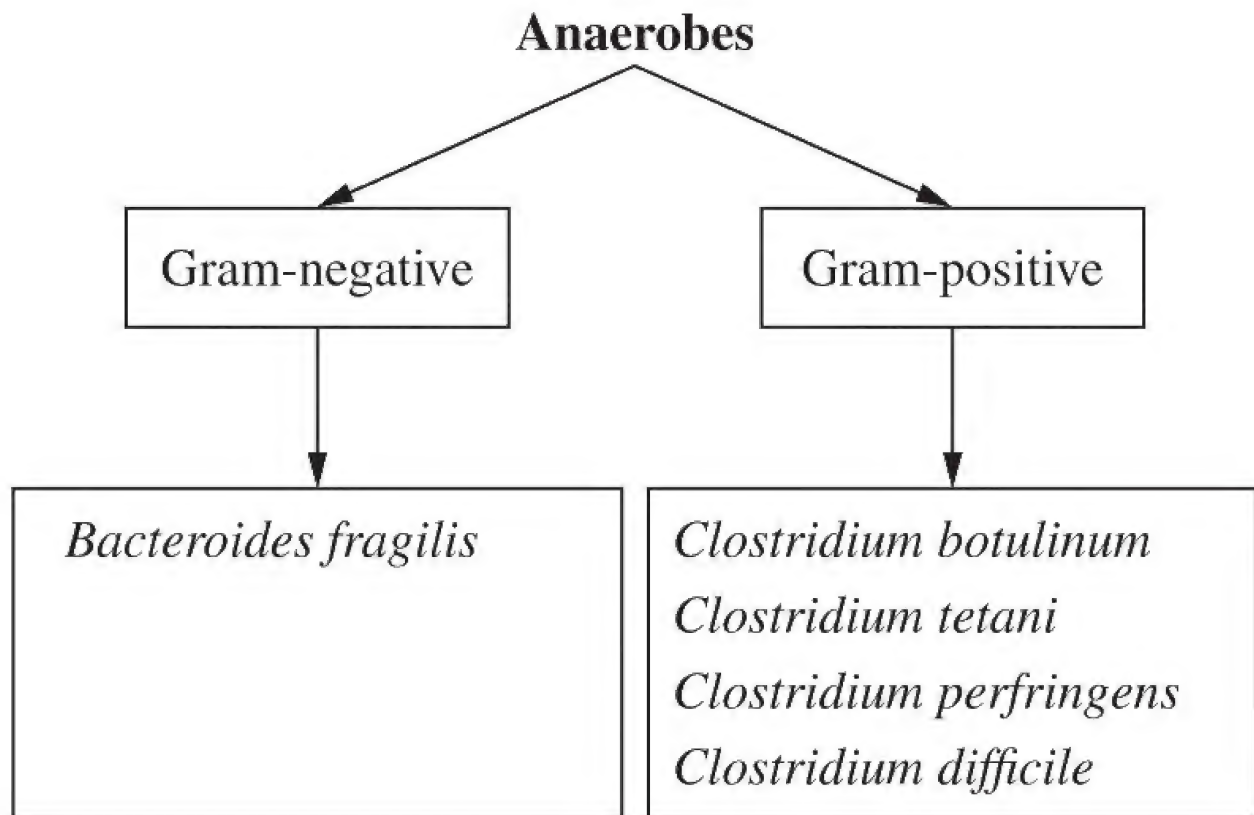
Organism and Physical Characteristics:	<i>Pseudomonas aeruginosa</i> Motile gram-negative rod. An aerobe that grows readily on many types of culture media.
Etiology and Epidemiology	This ubiquitous organism can be found in soil, water, plants, and food. It is a common contaminant on numerous objects in hospitals and can survive in many disinfectants.
Clinical Manifestations	<i>Pseudomonas aeruginosa</i> is opportunistic with major manifestations including wound infections in burn patients, recurring pneumonia in cystic fibrosis patients, pneumonia in severely ill, immunocompromised, and/or ventilated patients, bloodstream infections, and urinary tract infections, especially those associated with indwelling catheters.
Pathogenesis	Virulence factors include: endotoxin, exotoxin A, exoenzyme S, adhesins, and an antiphagocytic capsule. Host conditions that facilitate colonization are important, such as increased mucus production in lungs of cystic fibrosis patients that inhibits ciliary clearance, and burns that remove skin barriers. Overproduction of alginate in lungs of cystic fibrosis patients provides the matrix for survival in a biofilm, which can result in chronic infections. Exotoxin A is an A-B toxin with the same mechanism of protein synthesis inhibition and cell death as diphtheria toxin. Exoenzyme S is an ADP-ribosylating toxin that targets several cellular proteins.
Laboratory Diagnosis	When grown on normal laboratory media, <i>P. aeruginosa</i> gives off a fruity aroma. It also produces several pigments: pyocyanin gives a blue color to pus; pyoverdine is a yellow-green molecule that fluoresces under ultraviolet light and can be used to monitor burn patients for infection.
Treatment and Prevention	Antimicrobial susceptibility testing is important because <i>P. aeruginosa</i> can be resistant to many different antibiotics. Combination antibiotic therapy, such as an anti-pseudomonal beta-lactam with an aminoglycoside, might be used, depending on the organism susceptibility profile and the nature of the infection. Prevention involves methods for control of infection that are like those for other nosocomial pathogens.
Notes	

A 60-year-old man with a history of alcohol abuse is seen in the emergency room with a necrotizing pneumonia. Gram stain of a sputum sample reveals gram-negative encapsulated rods. A sample is sent to the laboratory for identification and antimicrobial susceptibility testing.

An Opportunistic Pneumonia

Organism and Physical Characteristics:	<i>Klebsiella pneumoniae</i> Gram-negative, nonmotile, lactose-fermenting rod, large mucoid capsule.
Etiology and Epidemiology	<i>K pneumoniae</i> are found in soil, water, and the large intestine. Colonization of the oropharynx can occur in individuals with compromised host defenses (alcoholics, the elderly, diabetes, chronic respiratory illness), malignancies, immunosuppression. Aspiration of organisms from the oropharynx leads to pneumonia.
Clinical Manifestations	Opportunistic pneumonia , necrotizing pneumonia, lower biliary tract, surgical wound sites, septicemia, osteomyelitis, meningitis, bacteremia, and urinary tract infections .
Pathogenesis	<i>K pneumoniae</i> possesses a variety of virulence factors including cell wall endotoxin, a thick mucoid capsule, and a variety of proteases.
Treatment and Prevention	<i>K pneumoniae</i> can be resistant to many antibiotics, so antimicrobial susceptibility testing is required. Resistance to cephalosporins, carbapenems, and polymyxins (colistin) is an emerging problem that will limit treatment choices.

Notes



KEY CONCEPTS

- Anaerobic bacteria do not use oxygen for growth and metabolism but obtain their energy from fermentation reactions. They require reduced oxygen tension for growth and fail to grow on the surface of solid medium in 10% CO₂ and ambient air.
- The ability of anaerobes to tolerate oxygen or grow in its presence varies from species to species. Less fastidious anaerobes have low levels of catalase

and/or superoxide dismutase. Most anaerobic infections of humans are caused by “moderately obligate anaerobes.”

- All *Clostridium* species form spores.

SUMMARY OF PATHOGENIC MECHANISMS OF ANAEROBES

Organism	Pathogenic mechanism
<i>Bacteroides fragilis</i>	Endogenous spread and abscess formation
<i>Clostridium botulinum</i>	Ingestion of preformed botulinum neurotoxin, flaccid paralysis Ingestion of spores, germination, multiplication and production of botulinum neurotoxin in the intestine of infants leading to flaccid paralysis
<i>Clostridium tetani</i>	Contamination of puncture wounds with spores followed by germination and production of the toxin, tetanospasmin, resulting in spastic paralysis
<i>Clostridium perfringens</i>	Contamination of wounds with spores followed by germination and production of tissue-destroying alpha toxin. Ingestion of spores and production of enterotoxin upon germination
<i>Clostridium difficile</i>	Endogenous spread, colonization, and production of toxins A and B

A 40-year-old woman experiences a sudden onset of dry mouth, muscle weakness, double vision, difficulty in swallowing, and difficulty in speaking. History revealed that she had eaten some home-canned green beans the night before. Samples of the beans and the patient’s serum are sent to the laboratory for toxin testing. The physician suspects botulism and gives the patient an injection of trivalent antitoxin.



Source: Centers for Disease Control and Prevention, Washington, DC.

Botulism

Organism and Physical Characteristics:	<i>Clostridium botulinum</i> Gram-positive anaerobic rod. Motile. Forms terminal endospores. Spores are heat-resistant.
Etiology and Epidemiology	Contamination facilitated by spore formation. Spores present in soil and on vegetables, survive improper canning, germinate, and produce toxin. Infant botulism is associated with the ingestion of spore-contaminated honey.
Clinical Manifestations	<i>C. botulinum</i> is the causative agent of botulism. Three manifestations are recognized: foodborne botulism , infant botulism , and wound botulism . Characterized by flaccid paralysis of voluntary and respiratory muscles. Infant botulism is thought to contribute to sudden infant death syndrome (SIDS). Most people who develop wound botulism inject drugs (eg, black tar heroin).
Pathogenesis	Infant botulism results from ingestion of spores followed by germination and toxin production in the intestine. Foodborne botulism results from ingestion of preformed toxin in food. Wound botulism results from contamination of wounds with spores or injection of spore-contaminated drugs. The major virulence factor is botulinum neurotoxin of which there are at least seven types (type A-G); most common types are A, B, and E. The toxins are zinc-dependent metalloproteases that specifically cleave SNARE proteins (VAMP, syntaxin, SNAP-25) preventing the neuron from releasing the neurotransmitter acetylcholine at neuromuscular synapses. This stops nerve signaling and results in flaccid paralysis.
Laboratory Diagnosis	Botulinum toxin is tested using a mouse bioassay for toxin in serum or food. ELISA and mass spectrometry are also used. Anaerobic culture of food or feces is also used.
Treatment and Prevention	Administration of trivalent (A, B, E) or heptavalent (A–G) antitoxins will neutralize the toxins. Mechanical ventilation is used with those experiencing paralysis. Prevention involves adequate food preparation, avoidance of suspected contaminated canned foods, and not feeding honey to infants less than 1 year of age.

Notes

A 36-year-old carpenter is seen in the emergency room with complaints of jaw and neck stiffness. History reveals that he stepped on a nail the previous week and received a deep puncture wound. He does not remember having any vaccinations in the last 30 years. He is given shots of tetanus antitoxin and tetanus toxoid and begun on a course of penicillin. The wound is surgically debrided.



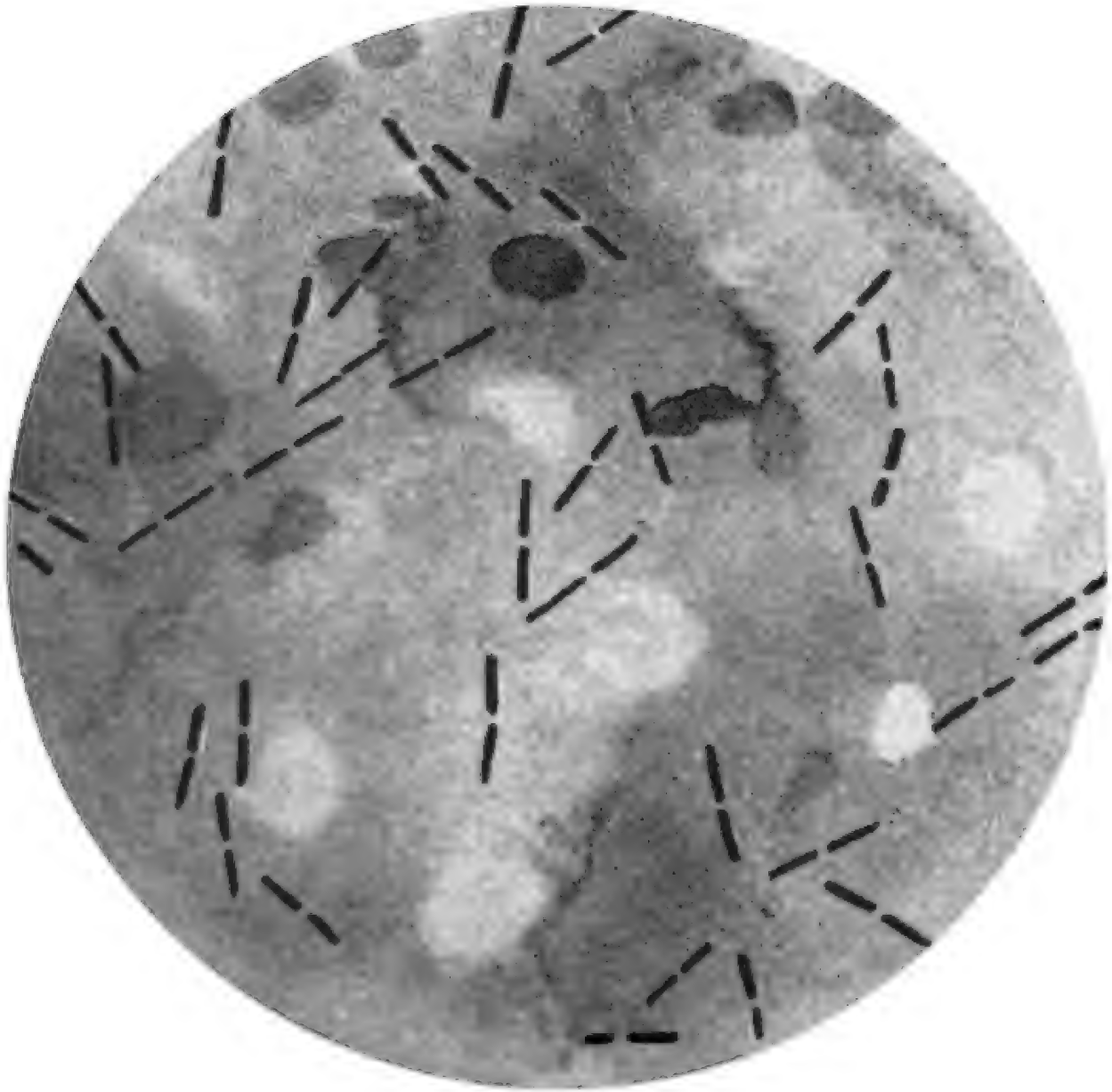
Source: Centers for Disease Control and Prevention, Washington, DC.

Tetanus from a Puncture Wound

Organism and Physical Characteristics:	<i>Clostridium tetani</i> Gram-positive, motile, anaerobic rod. During sporulation, spores will resemble a tennis racket or drumstick due to the presence of a terminal spore.
Etiology and Epidemiology	Transmission is most often associated with deep puncture wounds into which spores contaminating soil are inoculated. The spores subsequently germinate and the vegetative cells undergo replication. Other infections result from contaminated injuries, severe burns, and nonsterile surgery.
Clinical Manifestations	<i>C. tetani</i> is the causative agent of tetanus . Tetanus is characterized by spastic paralysis often manifested as a rigid smile (risus sardonicus), lockjaw (trismus), arching of the back (opisthotonus), and respiratory muscle spasms.
Pathogenesis	The major virulence factor is a neurotoxin called tetanospasmin . Tetanospasmin, a zinc-dependent metalloprotease, is carried to the central nervous system by retrograde axonal transport. The toxin specifically cleaves synaptobrevin II , which inhibits the docking of inhibitory neurotransmitter vesicles at synapses and results in continuous firing and severe muscle spasms.
Treatment and Prevention	Treatment involves supportive therapy and passive immunization with tetanus antitoxin in combination with antibiotics such as penicillin. Prevention involves active immunization with tetanus toxoid.

Notes

Sixteen hours after attending a school reunion at a local park, a 38-year-old male experiences abdominal cramps and watery diarrhea. One day later the symptoms have spontaneously resolved and he was able to go back to work. Food poisoning is suspected.



Source: Centers for Disease Control and Prevention, Washington, DC.

Food Poisoning

Organism and Physical Characteristics:	<i>Clostridium perfringens</i> Gram-positive, nonmotile, anaerobic rod. Spore formation. Five serotypes (A–E) are recognized based on the types of extracellular toxins (alpha, beta, epsilon, and iota) they make and their tropism. Grows rapidly with a division time of 6–8 minutes.
Etiology and Epidemiology	Spores are found in soil and in the colon of many animals and humans. Transmission is primarily through wound contamination and by ingestion of contaminated foods.
Clinical Manifestations	Two major clinical manifestations are gas gangrene (clostridial myonecrosis) and food poisoning . Other <i>Clostridium</i> species (<i>C. septicum</i> , <i>C. histolyticum</i>) can also cause gas gangrene.
Pathogenesis	The major virulence factor in gas gangrene is the production of alpha toxin (a phospholipase C) that causes damage to membranes, tissues, bleeding, and increased vascular permeability that can lead to systemic spread of the toxin. Collagenases, hyaluronidase, fibrinolysin, hemagglutinin, and hemolysins are also produced. Food poisoning results from enterotoxin production during sporulation.
Treatment and Prevention	Gangrene is life threatening and requires surgical intervention and high doses of antibiotics such as penicillin G. Food poisoning is self-limiting, usually requiring only supportive measures and fluid replacement. Prevention involves timely surgical debridement of traumatic injuries and good surgical practices. Food poisoning is best prevented by using proper food handling practices.
Notes	

A 28-year-old man has been taking clindamycin while hospitalized for nearly 2 weeks. He recently started to experience abdominal cramping and watery diarrhea. The attending physician decided to discontinue the antibiotics to see if the diarrhea would resolve. A stool sample was sent to the laboratory for ELISA testing for toxins A and B.

Hospital-Associated Diarrhea

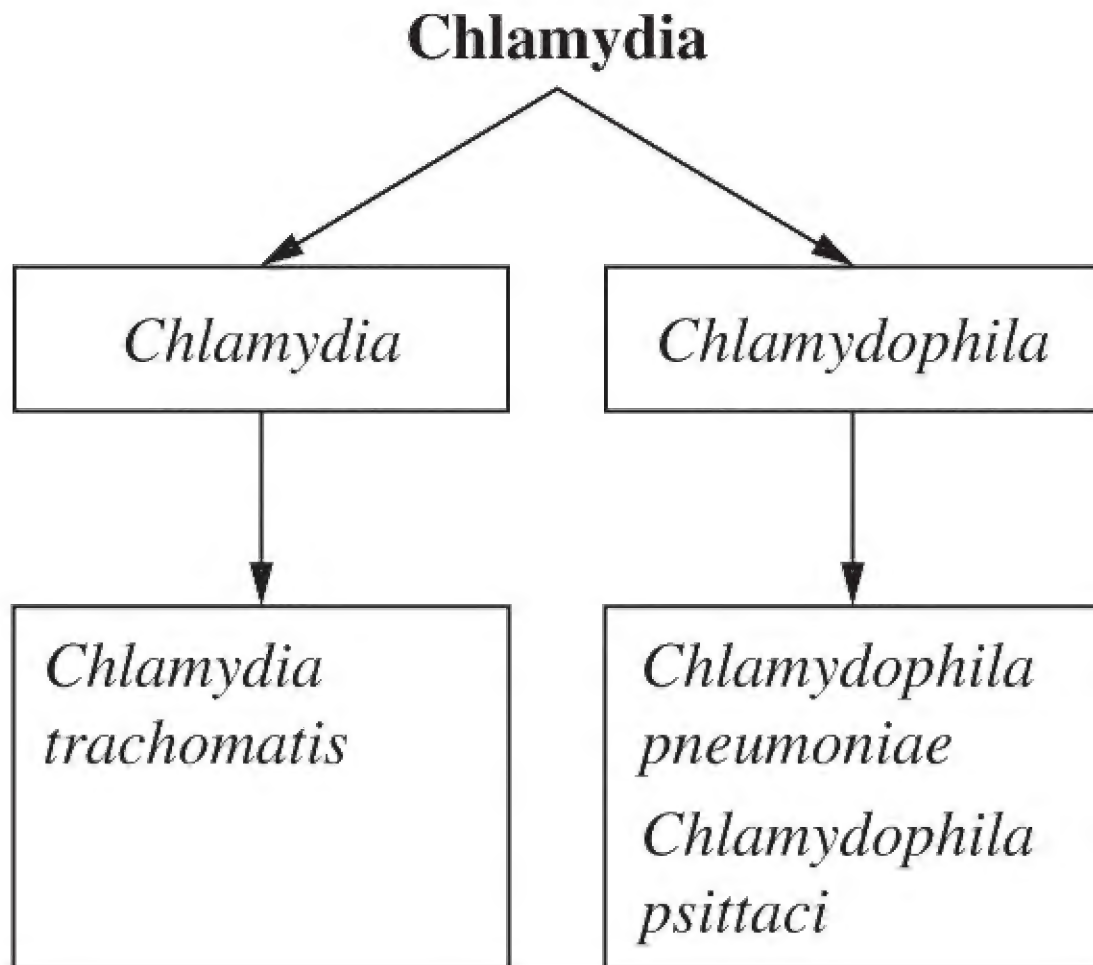
Organism and Physical Characteristics:	<i>Clostridium difficile</i> Gram-positive, motile, anaerobic rod. Ubiquitous in nature, prevalent in soil. Spore formation.
Etiology and Epidemiology	Transmission is most often through endogenous spread. Can be transmitted person to person by fecal-oral route. <i>C. difficile</i> is a minor component of the normal flora, but colonization is associated with antibiotic use that kills the normal flora, enabling overgrowth of <i>C. difficile</i> .
Clinical Manifestations	<i>C. difficile</i> is a common cause of antibiotic-associated diarrhea, pseudomembranous colitis, toxic megacolon, perforation of the colon, and sepsis.
Pathogenesis	The major virulence factors are two exotoxins called toxin A and toxin B. Toxin A is a potent enterotoxin with some cytotoxic activity whereas toxin B is a cytotoxin. Toxins A and B are glucosyltransferases that target and inhibit the Rho family of GTPases. The result of toxin activity is fluid secretion, cell death, and inflammation leading to pseudomembrane formation in the colon.
Laboratory Diagnosis	Toxin in stool can be assayed using enzyme-linked immunosorbent assays (ELISA) or with a cytotoxicity cell culture assay. Culture on selective medium coupled with testing colonies for toxin production is also used but requires a longer period of time for results.
Treatment and Prevention	Initial treatment involves discontinued use of antibiotics. More serious manifestations such as pseudomembranous colitis require antibiotic treatments such as metronidazole or vancomycin. Toxic megacolon may require surgery. Prevention involves careful monitoring of antibiotic use. Infection control protocols minimize the risk of transmission.
Notes	

A 20-year-old man is hospitalized after an automobile accident. While in the

hospital, he develops an intra-abdominal abscess. A sample of the abscess drainage was sent to the laboratory for aerobic and anaerobic culture. Preliminary laboratory results revealed a mixture of organisms including a gram-negative anaerobe.

Intra-Abdominal Abscess

Organism and Physical Characteristics:	<i>Bacteroides fragilis</i> Gram-negative rod, anaerobe.
Etiology and Epidemiology	<i>B fragilis</i> is part of the normal flora of the colon and vagina. Infections most often occur through endogenous spread following trauma.
Clinical Manifestations	<i>B fragilis</i> can be involved in a variety of polymicrobial or monomicrobial infections including intra-abdominal abscesses, peritonitis, gynecologic infections, and sepsis.
Pathogenesis	An antiphagocytic capsule facilitates escape from the innate immune system as well as abscess formation. Production of superoxide dismutase contributes to aerotolerance. <i>B fragilis</i> is often associated with mixed infections (polymicrobial) with other bacteria. Facultative growth from polymicrobial infections and tissue necrosis leading to a decreased blood supply contribute to an anaerobic microenvironment allowing proliferation.
Treatment and Prevention	In addition to abscess drainage, treatment with a combination regimen of antibiotics is often used for intra-abdominal abscesses because of the likelihood of a polymicrobial infection. One example of a regimen may consist of a third-generation cephalosporin (eg, ceftriaxone) plus metronidazole (latter for anaerobic coverage). Monomicrobial infection with <i>B fragilis</i> can be treated with metronidazole alone.
Notes	

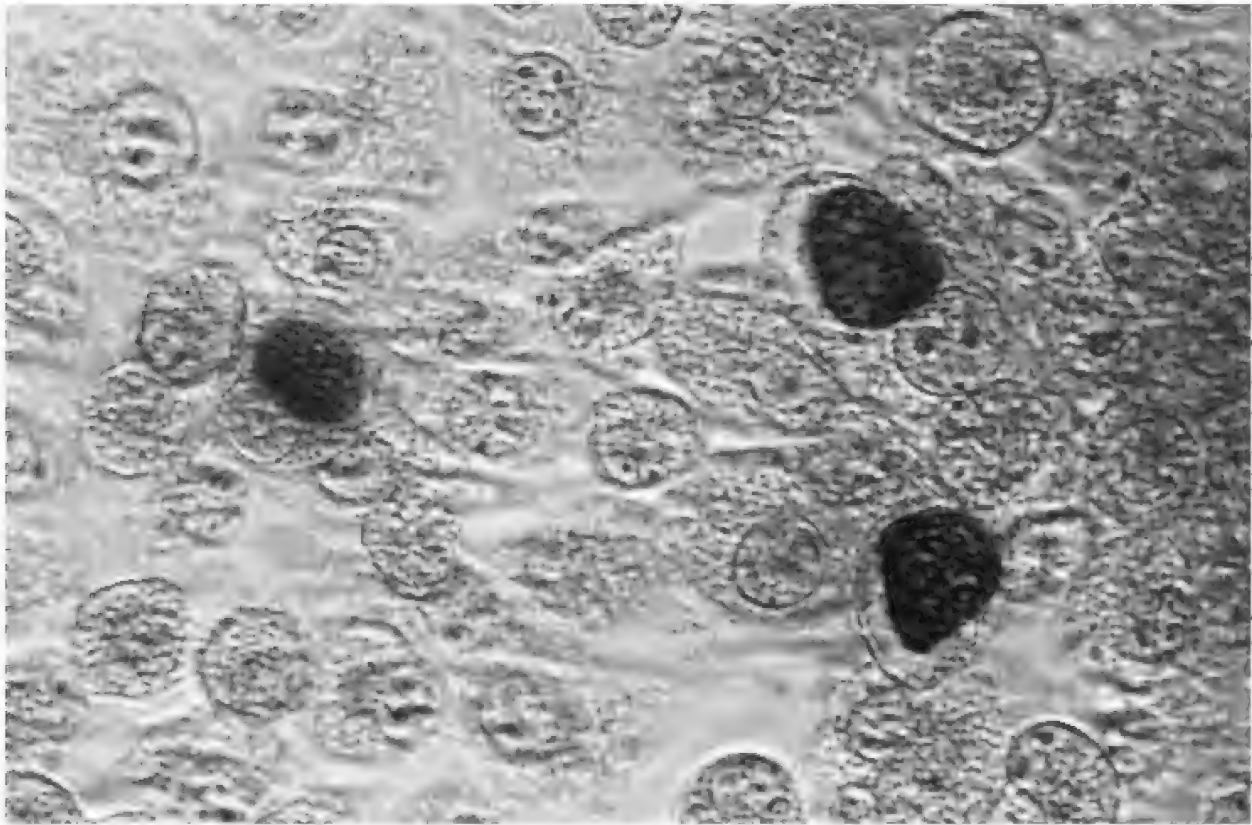


KEY CONCEPTS

- *Chlamydiae* are obligate intracellular parasites.
- The cell wall is like that of gram-negative organisms but does not contain a typical bacterial peptidoglycan.

- The life cycle of *Chlamydia* is comprised of two forms: the infectious form is called the elementary body and the metabolically active intracellular form is called the reticulate body.

A 24-year-old man presents to the STI clinic with painful urination and a non-purulent discharge. Gram stain of the discharge is negative for intracellular gram-negative diplococci. The man admits to being sexually active with multiple partners and does not always use a condom. The doctor obtains a urethral swab specimen and sends it to the laboratory for testing with a nucleic acid amplification assay. A 7-day course of doxycycline is begun.



Source: Centers for Disease Control and Prevention, Washington, DC.

Nongonococcal Urethritis (NGU)

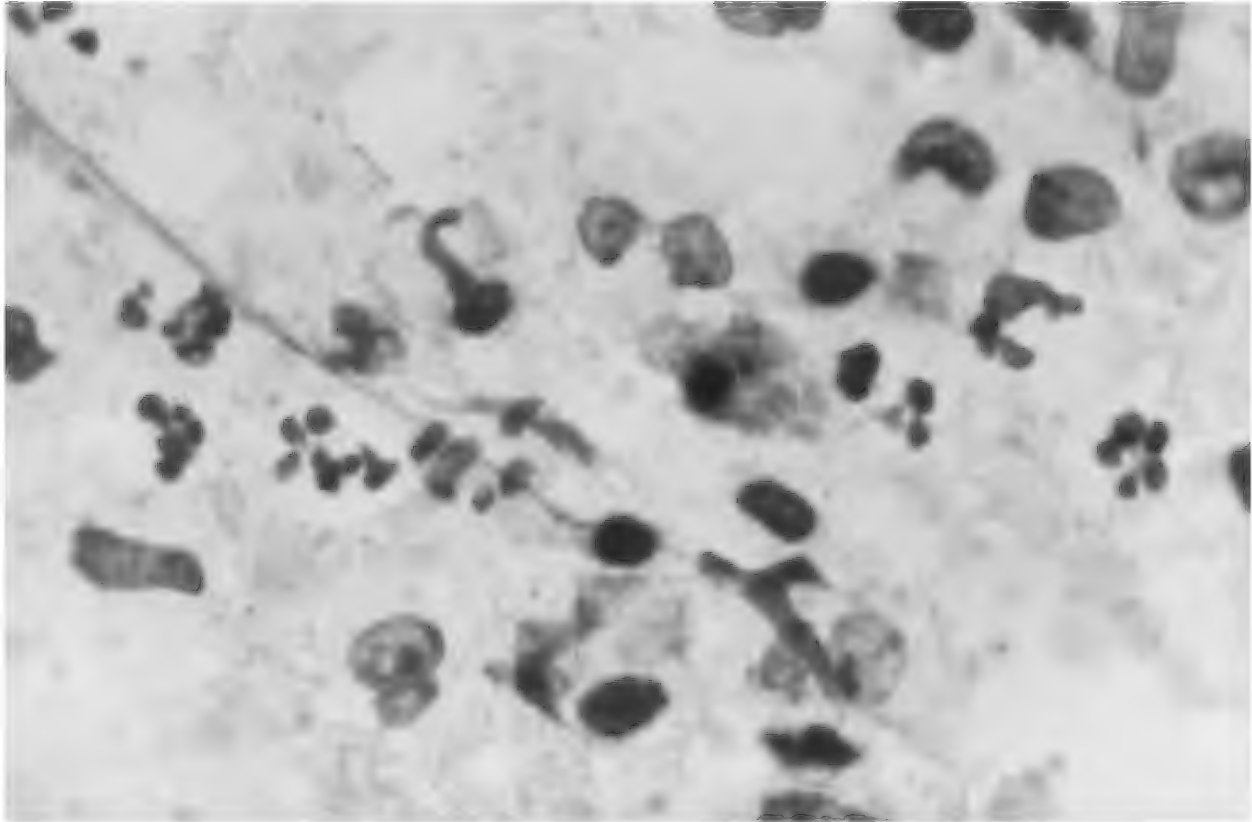
Organism and Physical Characteristics:	<i>Chlamydia trachomatis</i> Gram-negative-like cell wall lacking a typical peptidoglycan. Obligate intracellular parasite. Elementary body is the infectious extracellular form; reticulate body is the metabolically active intracellular form
Etiology and Epidemiology	Transmission is by direct contact. <i>C. trachomatis</i> is the most common bacterial sexually transmitted disease in the United States. There are at least 15 serovars of <i>C. trachomatis</i> that are associated with ocular and genital tract infections.
Clinical Manifestations	<i>C. trachomatis</i> causes several different diseases, including trachoma, inclusion conjunctivitis, infant pneumonia, nongonococcal urethritis, Reiter syndrome, lymphogranuloma venereum, salpingitis and pelvic inflammatory disease . Infants can become infected at birth from an infected birth canal. Ocular infections can be transmitted directly by fingers and by flies.
Pathogenesis	Tissue damage from the host inflammatory response is the main pathogenic mechanism. Repeated infections cause progressive inflammation and tissue damage, which can lead to blindness or infertility depending on the site of infection. Corneal scarring may follow infant conjunctivitis.
Laboratory Diagnosis	Cell culture, direct fluorescent antibody test, antigen detection assays (ELISA), and nucleic acid amplification assays are used in diagnosis.
Treatment and Prevention	Depending on the clinical manifestation, <i>C. trachomatis</i> can be treated with a variety of antibiotics including tetracyclines, macrolides, or fluoroquinolones. Prevention involves safe sex practices and prompt treatment of infections and avoidance of reinfection. Face washing and hygiene important for preventing trachoma.

A 54-year-old man is seen by his primary care doctor with a fever, headache, and a persistent dry unproductive cough. Chest X-ray reveals patchy infiltrates. Potential candidate causative agents include *Mycoplasma pneumoniae*, *Legionella pneumophila*, and *Chlamydophila pneumoniae*. A sputum sample is sent to the laboratory for culture identification and serologic analysis. In the meantime, a 14-day course of erythromycin is prescribed because of its effectiveness for all three agents.

Atypical Pneumonia

Organism and Physical Characteristics:	<i>Chlamydophila pneumoniae</i> Previously a member of the <i>Chlamydia</i> genus. Gram-negative-like cell wall lacking typical peptidoglycan. Obligate intracellular parasite. Elementary body is the extracellular infectious form; reticulate body is the intracellular metabolically active form.
Etiology and Epidemiology	Transmission is by respiratory droplets. Common cause of pneumonia around the world. A form of community acquired pneumonia. Typically acquired by otherwise healthy people. Organism can also infect reptiles, amphibians, and mammals.
Clinical Manifestations	<i>C pneumoniae</i> causes several respiratory illnesses including pharyngitis, bronchitis, and pneumonia . Infection is characterized by a persistent cough that can last weeks. Pneumonia is atypical and like that caused by <i>Mycoplasma pneumoniae</i> and <i>Legionella pneumophila</i> .
Laboratory Diagnosis	Serologic assays assist in diagnosis. Cell culture is also used. A nucleic acid amplification assay has recently received FDA approval.
Treatment and Prevention	<i>C pneumoniae</i> is sensitive to tetracyclines (doxycycline) and macrolides (erythromycin or azithromycin).
Notes	

A 22-year-old woman presents in the emergency room with fever, headache, chills, and a nonproductive cough. Chest X-ray reveals evidence of a bilateral interstitial pneumonia. History reveals the woman's job is to clean bird cages at a local pet store. The attending physician suspects that her illness is related to her occupation.



Source: Centers for Disease Control and Prevention, Washington, DC.

Psittacosis

Organism and Physical Characteristics:	<i>Chlamydophila psittaci</i> Previously a member of the <i>Chlamydia</i> genus. Gram-negative-like cell wall lacking typical peptidoglycan. Obligate intracellular parasite. Elementary body is the extracellular infectious form; reticulate body is the intracellular metabolically active form.
Biology and Epidemiology	Birds are natural reservoir of <i>C. psittaci</i> and transmission is by inhalation of dried bird droppings or handling of infected tissues. High-risk individuals include veterinarians, pet shop workers, bird handlers, and poultry workers.
Clinical Manifestations	Disease manifestations can be mild or severe. Mild manifestations include fever, headache, chills, malaise, myalgia, and bilateral interstitial pneumonia. Severe manifestations include hepatomegaly, splenomegaly, endocarditis, myocarditis, gastrointestinal symptoms, and encephalitis. Fatal cases have been reported but are rare.
Pathogenesis	Systemic organ involvement results from spread to the reticuloendothelial system and focal necrosis following entry into the respiratory tract.
Laboratory Diagnosis	Serology is used in diagnosis. PCR assays have been developed and can be performed in reference laboratories.
Treatment and Prevention	<i>C. psittaci</i> is typically treated with a tetracycline (doxycycline or tetracycline) or a macrolide (such as erythromycin).

Spirochetes



Borrelia burgdorferi
Borrelia recurrentis
Borrelia hermsii
Treponema pallidum
Leptospira interrogans

KEY CONCEPTS

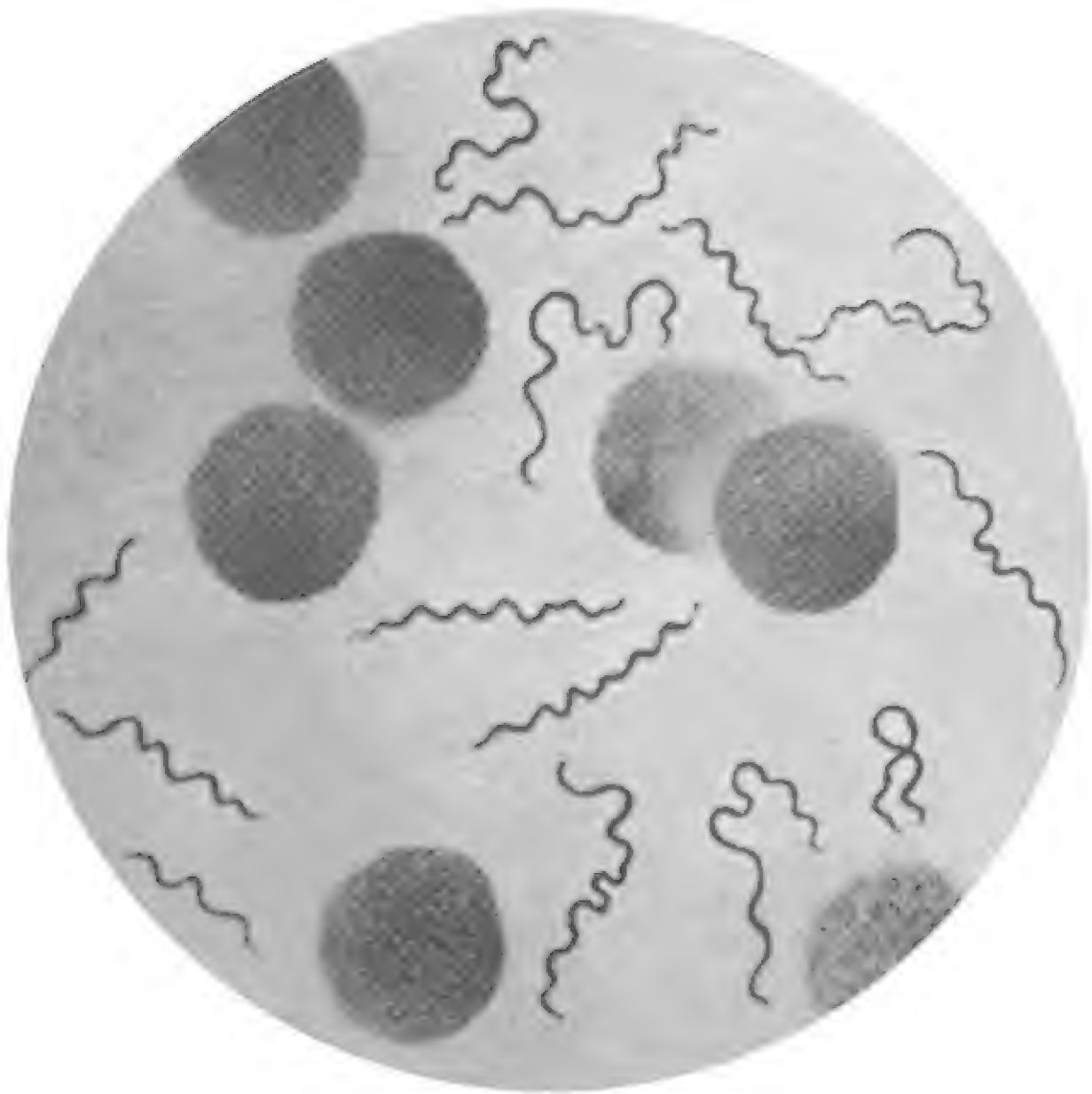
- Spirochetes are a large heterogeneous group of gram-negative, motile, thin-walled spiral-shaped bacteria.
- Pathogenic treponemes (eg, *Treponema pallidum*) have not been cultured continuously on artificial medium, in fertile eggs, or in tissue culture.
- Treatment of spirochete infections sometimes results in an abrupt onset of fever, chills, headache, and myalgias as a result of cell wall lysis and release of endotoxin. This phenomenon is known as the Jarisch-Herxheimer reaction.

A 12-year-old boy returns from a weekend camping trip in Connecticut. One week later, he stays home from school with complaints of flu-like symptoms that include fever, chills, headache, and myalgia. His mother notices a rash with a clear center that gets larger over the next couple of days. She remembers removing a tick from her son at the same spot where the rash has developed.

Lyme Disease

Organism and Physical Characteristics:	<i>Borrelia burgdorferi</i> Gram-negative, microaerophilic, motile spirochete.
Etiology and Epidemiology	Transmission from small mammal reservoirs occurs from bites of hard-bodied <i>Ixodes</i> ticks commonly known as the deer tick or black-legged tick. Prolonged exposure (24–48 hours) is required for efficient transmission. Transmitted to humans in saliva of tick. Humans are dead-end hosts.
Clinical Manifestations	Causative agent of Lyme disease. Stage 1 disease is characterized by a bull's-eye rash (erythema migrans) with a clear center that may be accompanied by fever, chills, and myalgias. Stage 2 disease occurs weeks to months later with manifestations that may include limb numbness , Bell's palsy , meningitis , encephalitis , and myocarditis . Stage 3 disease may occur months to years later and includes chronic skin , nervous system , or joint involvement .
Laboratory Diagnosis	The most common method of diagnosis is with serologic assays, including antibody titers, enzyme-linked immunosorbent assay (ELISA), and polymerase chain reaction (PCR). Spirochetes can be observed by darkfield microscopy and in stained preparations of thin or de-hemoglobinized thick smears of peripheral blood.
Treatment and Prevention	Treatment strategies depend on symptoms and stage but include antibiotics such as penicillin, aminopenicillin, or cephalosporin (eg, penicillin G, amoxicillin, or ceftriaxone, respectively) or a tetracycline (doxycycline). Prevention involves avoiding tick bites, prompt removal of ticks, use of insect repellants, and protective clothing barriers. A vaccine is available for high-risk individuals.
Notes	

After spending three nights in a rodent-infested cabin in Colorado, a 13-year-old boy experiences an abrupt onset of fever and chills. The symptoms last for 7 days and then resolve. Three days later, the fever returns. The mother takes him to their primary care doctor who prescribes an antibiotic.



Source: Centers for Disease Control and Prevention, Washington, DC.

Louse- and Tick-borne Relapsing Fever

Organism and Physical Characteristics:	<i>Borrelia recurrentis</i> and <i>Borrelia hermsii</i> Gram-negative spirochete.
Etiology and Epidemiology	<i>B. recurrentis</i> is transmitted person-to-person by the human body louse and <i>B. hermsii</i> (also <i>B. duttonii</i> and <i>B. parkeri</i>) is transmitted by the soft-bodied tick <i>Ornithodoros hermsii</i> .
Clinical Manifestations	Causative agents of relapsing fever. Symptoms include abrupt fever, chills, myalgias, and headache that may be accompanied by splenomegaly and hepatomegaly. Fever episodes last about a week, resolve for 3–7 days and then recur. Relapsing episodes usually occur 1–4 times. Mortality rate for louse-borne relapsing fever is 1% with treatment and 30%–70% without treatment.
Pathogenesis	Disease symptoms result from endotoxin in blood. Antibodies formed to bacterial outer membrane proteins resolve symptoms. Antigenic variation of the outer membrane proteins of spirochetes sequestered in liver and spleen accounts for the recurrent nature of the disease.
Laboratory Diagnosis	Observation of spirochetes by darkfield microscopy, and in Wright-, Giemsa-, or acridine orange-stained preparations of thin or de-hemoglobinized thick smears of peripheral blood. Polymerase chain reaction (PCR) are available.
Treatment and Prevention	Antibiotics such as penicillin or a cephalosporin (eg, ceftriaxone), a tetracycline (doxycycline or tetracycline), or a macrolide (erythromycin) are believed to be effective.
Note	

An 18-year-old San Diego man returns from a weekend trip with his friends to New Orleans during Mardi Gras. Three weeks later he develops a painless ulcer on his penis. He goes to a STI clinic where he is examined. History revealed that he had unprotected intercourse with multiple sexual partners while in New Orleans. He is given a single dose of benzathine penicillin G intramuscularly and counseled on safe sex practices.

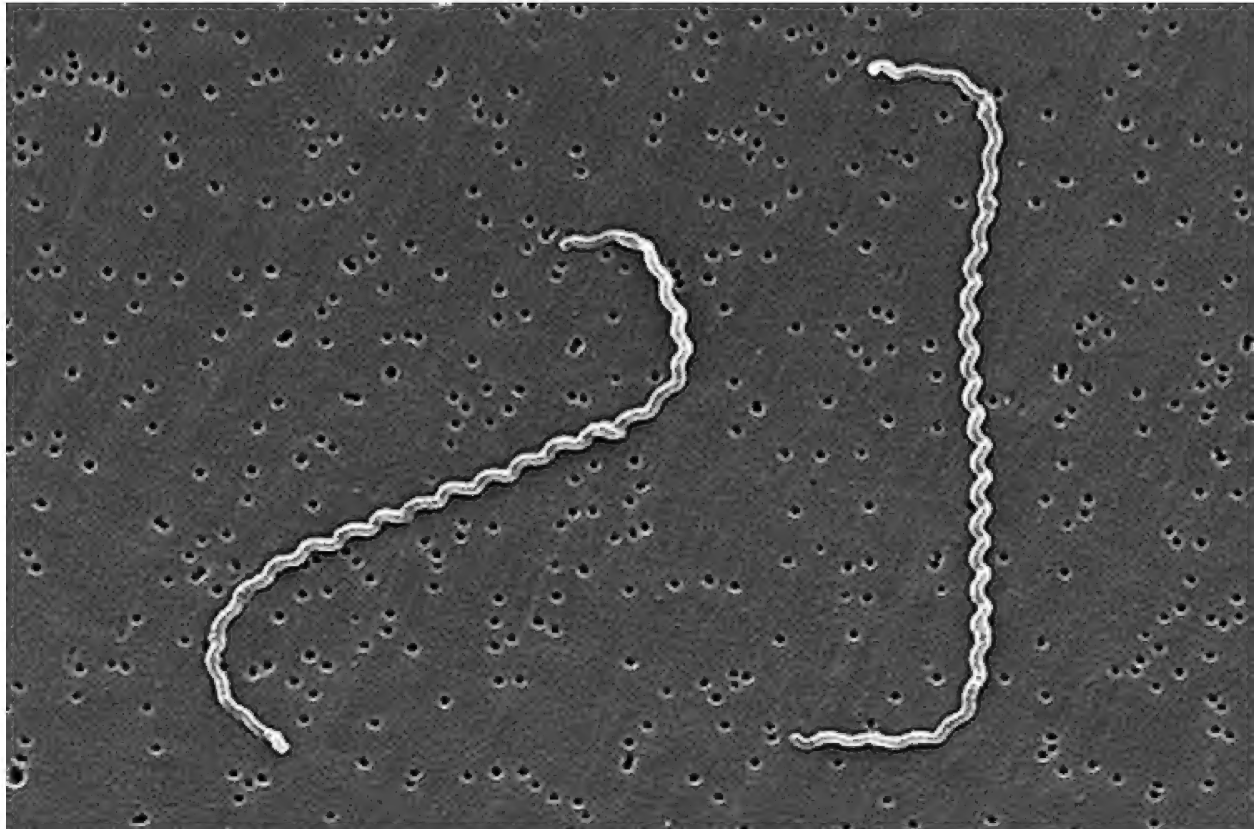


Source: Centers for Disease Control and Prevention, Washington, DC.

Primary Syphilis

Organism and Physical Characteristics:	<i>Treponema pallidum</i> subspecies <i>pallidum</i> Gram-negative, motile spirochete. Other subspecies are responsible for treponemal diseases such as yaws, bejel, and pinta.
Etiology and Epidemiology	<i>T pallidum</i> subspecies <i>pallidum</i> is usually transmitted through sexual contact. However, transplacental spread can cause congenital infections. Both primary and secondary lesions are highly infectious.
Clinical Manifestations	Causative agent of syphilis. Four common forms of disease include primary, secondary, tertiary, congenital syphilis. Primary syphilis is characterized by a painless ulcer or chancre that resolves spontaneously. Secondary syphilis is a disseminated manifestation that occurs 1–3 months after primary infection and is characterized by a maculopapular rash that can cover the entire body and moist papular lesions on mucous membranes and genitals (condylomata lata). Tertiary syphilis can develop decades later with multiple organ involvement including granulomas (gummas) in skin and bone, chronic meningitis, dementia, and aortic aneurysms. Congenital infection can lead to miscarriage or stillbirth. Infants born with syphilis can have deformities, neurologic and cardiac abnormalities.
Laboratory Diagnosis	<i>T pallidum</i> cannot be grown in cell-free culture. It can be visualized by dark-field microscopy or direct fluorescence assays. Serology for nontreponemal antigens (RPR and VDRL tests) and treponemal antigens (eg, FTA-ABS and MHA-TP) are used in diagnosis. Nontreponemal antibody will rise with infection and fall with successful treatment. Treponemal antibody titers confirm the nontreponemal tests and will remain positive for life.
Treatment and Prevention	Benzathine penicillin is used for treatment. Treatment of a pregnant woman cannot reverse any deformities, brain, or permanent tissue damage that have already occurred. Prevention involves safe sex practices and early diagnosis and treatment.
Notes	

On her vacation in Puerto Rico, a 28-year-old woman spent a lot of time exploring rainforests and swimming in freshwater pools. One week after returning she experiences a flu-like illness with fever, chills, and myalgias. The symptoms subside and then about 3 days later she exhibits an extreme headache and stiff neck. Cerebrospinal fluid collected at the emergency room is negative for bacteria.



Source: Centers for Disease Control and Prevention, Washington, DC.

Leptospirosis

Organism and Physical Characteristics:	<i>Leptospira interrogans</i> Gram-negative, motile spirochete. Obligate aerobe.
Etiology and Epidemiology	Transmission is through direct contact with infected animal urine or by exposure to water or soil contaminated with urine from infected animal reservoirs such as dogs, cattle, rodents, and other wild animals. Spirochetes enter through scratches or breaks in the skin. Two clinically recognizable syndromes: anicteric and icteric.
Clinical Manifestations	<i>L. interrogans</i> causes leptospirosis. Most infected persons will present with the anicteric form, which is flu-like with fever, chills, and myalgia. There may be a second immune-mediated phase classically known as the biphasic clinical course. Some will present with the more serious icteric form (ie, Weils disease), associated with extensive vascular damage often resulting in hepatic and renal failure.
Pathogenesis	After entry through abraded skin and mucus membranes, spirochetes gain entry to the bloodstream, multiply, and spread to multiple tissues. Primary infections are cleared by the humoral immune response but immune complexes are formed during the second phase of disease.
Laboratory Diagnosis	Serology is used for diagnosis. Organisms can sometimes be cultured from blood or cerebrospinal fluid but only within a narrow window of infection.
Treatment and Prevention	Treatment depends on the severity of symptoms but includes antibiotics such as penicillin, amino penicillin (amoxicillin), third-generation cephalosporin (such as ceftriaxone or cefotaxime), tetracycline (doxycycline), or macrolide (azithromycin). Prevention involves prophylactic doxycycline for high-risk individuals and vaccines for domestic animals.
Notes	

Mycoplasma



Mycoplasma pneumoniae
Mycoplasma genitalium

KEY CONCEPTS

- *Mycoplasma* species do not contain cell walls and are therefore not susceptible to the action of antibiotics such as penicillins, cephalosporins, vancomycin, bacitracin, and cycloserine that target cell wall synthesis.
- The cell membrane is unique in that it is one of the few prokaryotic membranes to contain sterols.
- *Mycoplasma* is the smallest free-living bacteria.

A 15-year-old boy is taken to the family's primary care doctor because of a "cold" that has lasted several weeks. On examination, the boy has a low-grade fever and mild shortness of breath that has lasted several days. He has recently developed a dry, nonproductive cough. Microscopic examination of a Gram-stain of his sputum reveals neutrophils but no bacteria. Chest X-ray reveals patchy infiltrates. The patient is started on a course of azithromycin.

Atypical Pneumonia

Organism and Physical Characteristics:	<i>Mycoplasma pneumoniae</i> Cell wall deficient. Cell membrane contains sterols.
Etiology and Epidemiology	Transmission is by infectious aerosols.
Clinical Manifestations	Also, known as Eaton agent, <i>M. pneumoniae</i> causes both upper and lower respiratory infections. Upper respiratory infections include pharyngitis, otitis media, and tracheobronchitis. Lower respiratory disease is known as primary atypical pneumonia.
Pathogenesis	<i>M. pneumoniae</i> has one primary virulence factor called the P1 adhesin protein, which binds to ciliated epithelial cells causing ciliostasis, cell destruction, and reduced ciliated clearance.
Laboratory Diagnosis	Diagnosis is largely made by clinical recognition of the syndrome. Laboratory tests are of secondary value. Serology may be useful in diagnosis.
Treatment and Prevention	Treatment includes antibiotics such as a macrolide (azithromycin or erythromycin) or a tetracycline (doxycycline or tetracycline). Because there is no cell wall, antibiotics that inhibit cell wall synthesis such as penicillins, cephalosporins, and vancomycin are not recommended.
Notes	

A 27-year-old man had unprotected intercourse with a new sexual partner. Two weeks later he developed a mucopurulent urethral discharge and burning on urination. He sought treatment at an STI clinic where a urethral swab specimen and smear were obtained and sent to the laboratory for testing. Examination of a Gram-stained smear revealed PMNs but no intracellular diplococci. Nucleic acid amplification test results for *Chlamydia trachomatis* and *Neisseria gonorrhoeae* were negative. The patient is prescribed a single dose of azithromycin.

Nonchlamydial, Nongonococcal Urethritis

Organism and Physical Characteristics:	<i>Mycoplasma genitalium</i> Cell wall deficient. Cell membrane contains sterols.
Etiology and Epidemiology	A significant cause of nongonococcal, nonchlamydial urethritis in men and women. Also, a cause of cervicitis and pelvic inflammatory disease including endometritis and salpingitis. Transmission is by sexual contact.
Clinical manifestations	Symptoms in men, when present, include urethral discharge and burning on urination. Infections may be acute or chronic. Symptoms in women, when present, include vaginal itching, burning on urination, and pain during intercourse.
Pathogenesis	Little is known about the virulence factors of <i>M. genitalium</i> .
Laboratory Diagnosis	<i>M. genitalium</i> is very difficult to culture. PCR may be available in some reference laboratories. Diagnosis involves ruling out <i>Neisseria gonorrhoeae</i> and <i>Chlamydia trachomatis</i> .
Treatment and Prevention	Azithromycin most effective; however, azithromycin resistance can occur. Moxifloxacin may be used when azithromycin is ineffective due to antibiotic resistance.

Notes

Mycobacteria



Mycobacterium tuberculosis

Mycobacterium leprae

Mycobacterium avium-intracellulare
complex

KEY CONCEPTS

- The cell wall of mycobacteria is similar to gram-positive organisms but contains a high concentration of waxes and complex branched hydrocarbons known as **mycolic acids**. The cell wall is composed of peptidoglycan and an external lipid bilayer; the inner leaflet contains mycolic acids and the outer leaflet contains other lipids.
- The high lipid content of the cell wall prevents staining of the cell by the Gram reaction; the cell can be visualized by the acid-fast stain using either the Ziehl-Neelsen or Kinyoun staining method.
- The high lipid content also makes these organisms resistant to detergents and many different antibiotics.

- Mycobacteria that form colonies clearly visible to the naked eye within 7 days on subculture are termed rapid growers, while those requiring longer periods (weeks) are termed slow growers.
 - Exposure is monitored by cell-mediated immune responses to cell wall proteins (PPD for *M tuberculosis* and lepromin for *M leprae*).
-

A 28-year-old woman is seen in the emergency room with fever, night sweats, and coughing up blood. History reveals she is HIV positive and has lost over 10 pounds of weight unintentionally over the last month. A sputum sample is positive for acid-fast bacilli.



Source: Centers for Disease Control and Prevention, Washington, DC.

Tuberculosis

Organism and Physical Characteristics:	<i>Mycobacterium tuberculosis</i> Acid-fast rod, mycolic acids in cell wall, slow growing.
Etiology and Epidemiology	Transmission is by respiratory aerosols. Infectivity is high, leading to positive skin test conversion. Reactivation of disease occurs in immunocompromised hosts.
Clinical Manifestations	Causative agent of tuberculosis . Active pulmonary disease is characterized by cough, hemoptysis, fever, weight loss, and night sweats. The lungs can contain multiple granulomas with caseation . Disseminated or miliary tuberculosis results from tubercle erosion. Bacteria spread through the bloodstream and can produce granulomas in any organ. A high fatality rate is associated with <i>M. tuberculosis</i> chronic meningitis.
Pathogenesis	The primary pathogenic mechanism results from the ability of <i>M. tuberculosis</i> to survive and replicate in macrophages. This results in granuloma formation (tubercle) with caseous necrotic centers. Liquefaction of the caseous centers and cavitation accompany progression to active disease. Organisms can survive inside tubercles for years, leading to reactivation with immunosuppression (eg, HIV infection, immunosuppressive therapies).
Laboratory Diagnosis	For active disease, direct examination of sputum may reveal acid-fast bacilli. Exposure is monitored by reactivity to the PPD skin test, which is a cell-mediated immune response to the protein component of the cell wall (purified protein derivative, or PPD). Growth in culture is very slow (3–4 weeks) and requires special media but is important for susceptibility testing. Tests for detection of latent tuberculosis include PPD or the relatively newer <i>in vitro</i> blood tests known as interferon- γ release assays (IGRAs). IGRAs are based on detection of interferon- γ release by host immune cells upon exposure to <i>M. tuberculosis</i> antigens. Polymerase chain reaction (PCR) on select body fluids or tissues (eg, sputum, bronchoalveolar fluid, cerebrospinal fluid) provides a rapid assay for determination as to whether an infection with acid fast bacilli is due to <i>M. tuberculosis</i> or a non-tuberculosis mycobacterial species.
Treatment and Prevention	Combination therapy with antibiotics for prolonged periods (6–9 months) is used in treatment. Therapy is guided by susceptibility testing but, in general, may include isoniazid (INH), rifampin, ethambutol, pyrazinamide, streptomycin, ethionamide, cycloserine, and fluoroquinolones. Directly observed therapy (DOT) to ensure compliance is an important component of successful treatment. Multi-drug resistant (MDR) <i>M. tuberculosis</i> is defined as exhibiting resistance to at least isoniazid and rifampin, which are the two most potent first-line anti-tuberculosis drugs. Extensively-drug resistant (XDR) <i>M. tuberculosis</i> exhibits resistance to isoniazid and rifampin with additional resistance to at least one fluoroquinolone and one injectable agent (eg, amikacin, kanamycin, or capreomycin). Treatment courses are more prolonged for patients with MDR- or XDR- <i>M. tuberculosis</i> . Prevention strategies include vaccination (not in the United States) with a live mycobacterium from a related species (bacillus Calmette-Guerin, or BCG) and appropriate chemoprophylaxis for individuals with recent PPD conversions.

A 35-year-old Texan presents with numerous skin lesions on his face that have become progressively worse over the last year. The lesions exhibit loss of pain sensation and temperature sensitivity. A skin biopsy reveals numerous acid-fast bacilli that fail to grow in culture. A lepromin skin test comes back negative.

Leprosy (Hansen's disease)

Organism and Physical Characteristics:	<i>Mycobacterium leprae</i> Acid-fast rod. Mycolic acids in cell wall. Slow growing; does not grow on artificial medium.
Etiology and Epidemiology	Transmission is through person to person contact. Incubation period is probably 2–10 years. In the United States, most cases occur in Texas, California, Louisiana, and Hawaii. Armadillos can act as endemic reservoirs.
Clinical Manifestations	Two primary forms of leprosy are recognized: tuberculoid and lepromatous. Tuberculoid leprosy is characterized by macular skin lesions, peripheral nerve damage, and granuloma formation. Lepromatous leprosy is characterized with extensive tissue and nerve damage, and numerous infectious skin lesions.
Pathogenesis	<i>M. leprae</i> survive and replicate in macrophages (lepromatous form) and Schwann cells (tuberculoid form). In lepromatous leprosy, a specific cell-mediated immune response is lacking, allowing organisms to replicate and accumulate, resulting in extensive skin lesions and systemic spread. Tuberculoid skin lesions contain many granulomas but few organisms.
Laboratory Diagnosis	Diagnosis primarily a clinical one. <i>M. leprae</i> cannot be grown in cell-free culture. The lepromin skin test and microscopic examination of skin lesions can aid diagnosis. Lepromatous lesions contain many organisms and patients are generally lepromin negative (antibody response; B-cell mediated), whereas tuberculoid lesions contain few organisms and patients are lepromin positive (delayed type hypersensitivity; T-cell mediated).
Treatment and Prevention	Long-term combination therapy (up to several years) with antibiotics such as dapsone, rifampin, and clofazimine may be necessary to adequately treat leprosy. Exposed individuals may receive chemoprophylaxis.
Notes	

A 46-year-old HIV-positive man is seen in the emergency room with complaints of fever, chills, night sweats, and diarrhea. The patient's CD4+ T-cell count is 50, and he reports a progressive weight loss over the past several months. He had previously been treated for *Pneumocystis* pneumonia. A sputum sample is positive for acid-fast bacilli, and blood culture grows atypical mycobacteria.

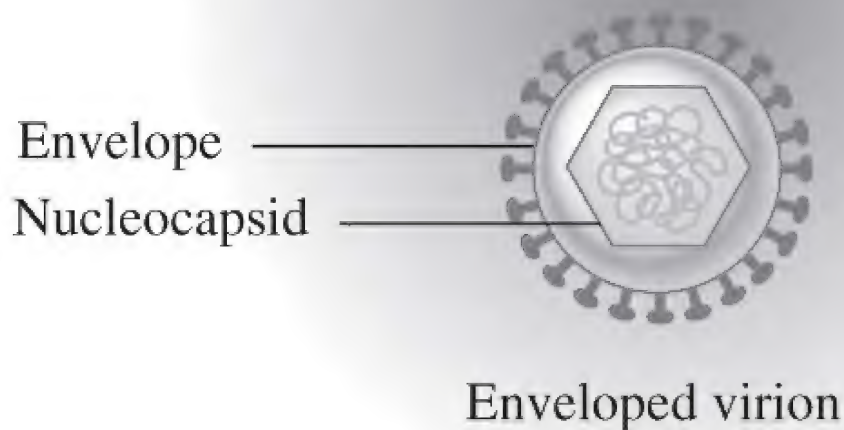
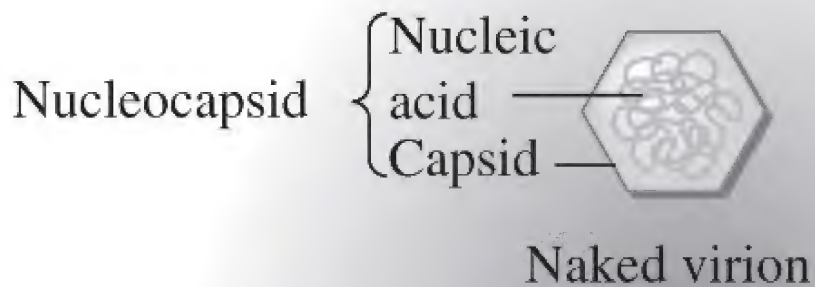
An Opportunistic Disseminated Disease

Organism and Physical Characteristics:	<i>Mycobacterium avium-intracellulare</i> Acid-fast rod; mycolic acids present in cell wall. Ubiquitous in the environment. Slow growing; optimum growth at 41°C.
Etiology and Epidemiology	Environmental exposure by ingestion or inhalation of organisms, which can be found in soil and water.
Clinical Manifestations	<i>M. avium-intracellulare</i> complex causes opportunistic pulmonary and disseminated disease in immunocompromised individuals. It is one of the most common systemic infections in patients with AIDS and is associated with high mortality rates. Risk of developing infection is greatly increased in those with low CD4 counts. A paradoxical worsening of a pre-existing infection due to <i>M. avium-intracellulare</i> , or other infectious agent, can occur when the host immune system regains the ability to mount an immune response. This syndrome is known as immune reconstitution inflammatory syndrome (IRIS) and usually requires addition of anti-inflammatory drugs.
Treatment and Prevention	Routinely resistant to first-line antituberculosis drugs. Clarithromycin or azithromycin plus ethambutol is preferred initial therapy.
Notes	

PROPERTIES OF VIRUSES

- Viruses are small, infectious, obligate parasites.
- Mature extracellular virus particles, called **virions**, are metabolically inert and mediate the transmission of the virus from host to host.
- The virion consists of a **genome** that may be either DNA or RNA, surrounded by a protein coat, or **capsid**.
- Intracellular viral replication requires disassembly of the virion, viral genome-directed synthesis of virion components by cellular machinery, and the assembly of progeny genomes and viral proteins to form new virions.

VIRUS ANATOMY



VIRION COMPONENTS AND FUNCTION

- Virions are composed of a genome and a protein capsid. The viral genome plus the capsid is termed the **nucleocapsid**.
- Some virions possess a host cell membrane-derived lipid **envelope** containing viral glycoproteins that surrounds the nucleocapsid.
- Viruses with envelopes are referred to as **enveloped** viruses; viruses without an envelope are called **naked** viruses.

- Capsids and envelopes serve to protect the viral genome in its extracellular state from physical and enzymatic destruction.
- Capsids and envelopes contain binding sites for attachment to cell receptors and mediate entry of the virion into susceptible cells.
- Some viruses contain **enzymes** (eg, virion polymerases) or other viral proteins necessary for efficient viral reproduction.
- The viral nucleic acid genome encodes information needed for viral replication and the synthesis of progeny virions.
- DNA virus genomes may be single-stranded (ss) or double-stranded (ds), linear or circular molecules.
- RNA virus genomes may be ss or ds, linear or circular, nonsegmented or segmented molecules.
- The ss viral RNA genomes are classified in two ways.
 - ▶ **Positive-strand (+) RNA viruses** denote that the genome is of the same polarity or sense as mRNA.
 - ▶ **Negative-strand (–) RNA viruses** signify that the genome is complementary to mRNA (ie, of negative polarity) and incapable of functioning as mRNA.

VIRION STRUCTURE

- Viral nucleocapsids have two types of symmetry: **helical and icosahedral**.
- Capsid symmetry is based on the arrangement of morphologic subunits called **capsomeres**. Capsomeres are composed of multiple copies of one or several different polypeptides that form the capsid.
- **Helical nucleocapsids** are composed of protein subunits bound to the viral RNA in the form of a helix. **Note:** Only RNA viruses have helical symmetry.
- **Icosahedral nucleocapsids** have protein subunits arranged in the form of an icosahedron with 20 triangular faces and 12 vertices. The viral nucleic acid is located inside the capsid shell.
- Some viruses have neither helical nor icosahedral symmetry and are designated structurally as **complex** (eg, poxviruses).

VIRUS CLASSIFICATION

- Viruses are classified by the nature of the nucleic acid (DNA or RNA), symmetry of the capsid (helical or icosahedral), presence or absence of an envelope, and size of the virion.

CLASSIFICATION OF HUMAN VIRUSES

DNA Viruses

Virus Family	Virus Example	Nucleic Acid	Nucleocapsid Symmetry	Envelope
Poxviridae	Smallpox virus	Linear ds DNA	Complex	Yes
Herpesviridae	Herpes simplex, cytomegalovirus	Linear ds DNA	Icosahedral	Yes
Adenoviridae	Adenovirus	Linear ds DNA	Icosahedral	No
Papillomaviridae	Papillomavirus	Circular ds DNA	Icosahedral	No
Polyomaviridae	JC virus	Circular ds DNA	Icosahedral	No
Parvoviridae	B19 virus	ss DNA	Icosahedral	No
Hepadnaviridae	Hepatitis B	Circular, partially ds DNA	Icosahedral	Yes

CLASSIFICATION OF HUMAN VIRUSES

RNA Viruses

Virus Family	Virus Example	Nucleic Acid	Nucleocapsid Symmetry	Envelope
Orthomyxoviridae	Influenza virus	Segmented ss RNA	Helical	Yes
Bunyaviridae	La Crosse virus, Hantavirus	Circular ss RNA; three segments	Helical	Yes
Arenaviridae	Lassa fever virus	Circular ss RNA; two segments	Helical	Yes
Picornaviridae	Poliovirus, rhinovirus, hepatitis A virus	Linear ss RNA	Icosahedral	No
Caliciviridae	Norovirus	Linear ss RNA	Icosahedral	No
Astroviridae	Astrovirus	Linear ss RNA	Icosahedral	No
Coronaviridae	Coronavirus	Linear ss RNA	Helical	Yes
Flaviviridae	West Nile virus, hepatitis C virus, Dengue virus, Zika virus	Linear ss RNA	Icosahedral	Yes
Togaviridae	Eastern equine encephalitis, rubella virus, Chikungunya virus	Linear ss RNA	Icosahedral	Yes
Retroviridae	HIV-1 & 2, HTLV-1 & 2	Linear ss RNA	Icosahedral	Yes
Reoviridae	Rotavirus	Segmented ds RNA	Icosahedral	No
Paramyxoviridae	Parainfluenza, measles, mumps	Linear ss RNA	Helical	Yes
Rhabdoviridae	Rabies virus	Linear ss RNA	Helical	Yes
Filoviridae	Ebola and Marburg viruses	Linear ss RNA	Helical	Yes

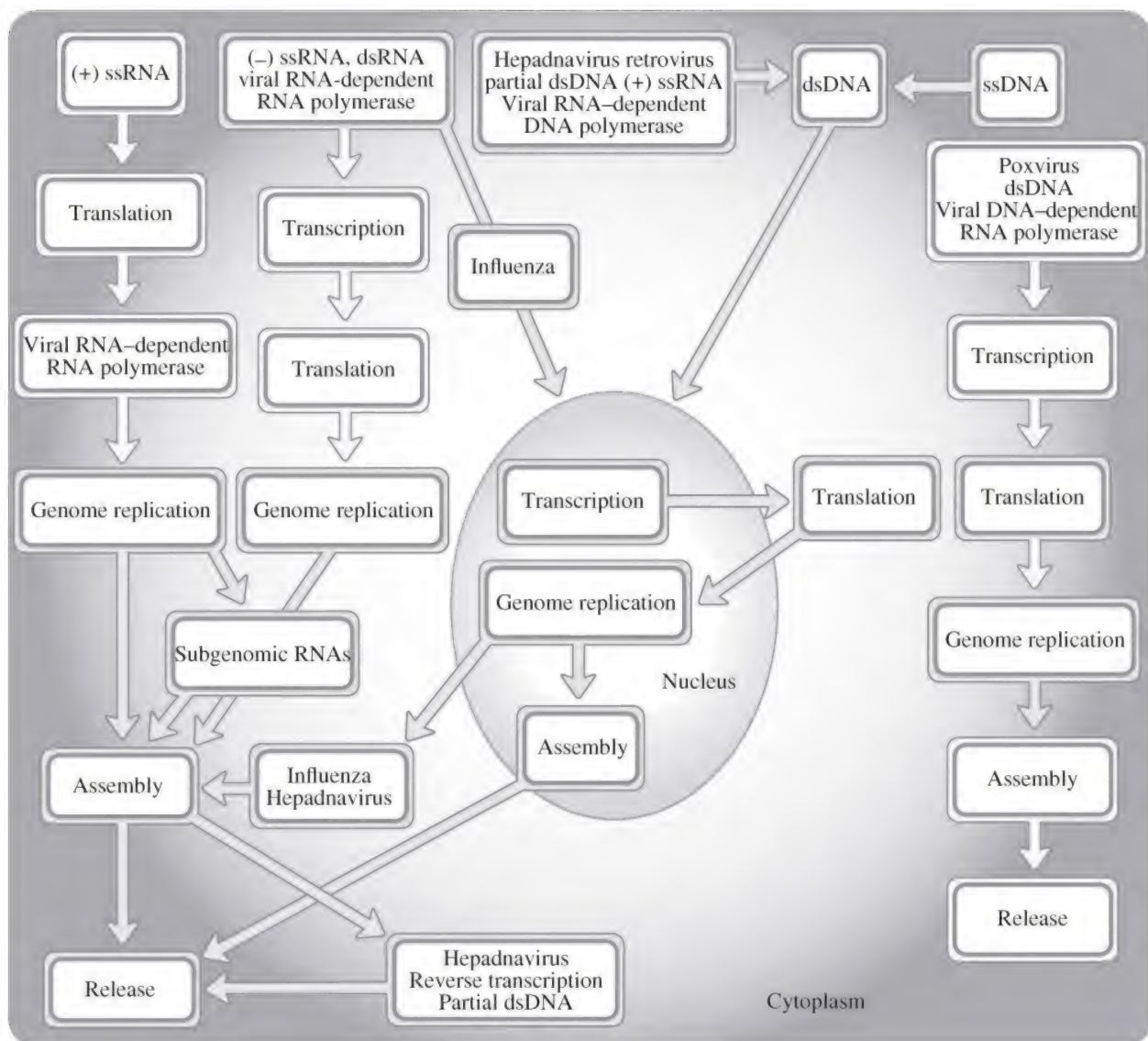
VIRAL REPLICATION

Virus Life-Cycle

- **Attachment:** Viruses attach to specific cell receptors via **viral attachment proteins (VAPs)** on the viral capsid or envelope (eg, hemagglutinin of influenza virus, gp120 of HIV-1). Examples of cell receptors for VAPs: sialic acid (influenza virus) and CD4 (HIV-1).
- **Penetration and uncoating:** **Direct membrane fusion** and **receptor-mediated endocytosis** are mechanisms of virus entry into cells.
- **Viral gene expression:** Production of viral mRNA from the viral genome that encodes proteins needed for genome replication and synthesis of progeny virus.

- **Nucleic acid replication:** All DNA viruses except poxvirus replicate their genome in the nucleus. All RNA viruses except influenza virus and retroviruses replicate in the cytoplasm.
- **Assembly and release:** Newly synthesized capsid proteins self-assemble and package the viral nucleic acid. Enveloped viruses acquire their envelope by budding through the plasma membrane or nuclear membrane (herpesviruses). Virions are released by cell lysis (nonenveloped viruses) or by budding from the plasma membrane (enveloped viruses).

REPLICATION STRATEGIES OF DNA AND RNA VIRUSES



VIRUS-CELL INTERACTIONS

- **Lytic infections:** Characterized by virion production and death of the permissive host cell (eg, rhinovirus and norovirus infections).
- **Abortive infections:** Characterized by no virion production and host cell survival.
- **Persistent infections:** Characterized generally by cell survival with or without production of infectious viruses.
 - ▶ **Chronic infections:** Characterized by nonlytic, continuous shedding of virus from the infected cell (eg, hepatitis B virus).
 - ▶ **Latent infections:** Characterized by no production of progeny virus but the virus genome remains quiescent in the cell for months or years with later virus production by reactivation (eg, herpesviruses).
 - ▶ **Transforming infections:** Characterized by the acquisition of growth, morphologic, and behavioral properties of tumor cells (eg, papillomaviruses and human T-cell leukemia virus).
- **Slow infections:** Characterized by the slow (years to decades) clinical course, accumulation of misfolded prion protein in the brain resulting in neuronal degeneration and spongiform encephalopathy (eg, prion diseases). Prions are not viruses. They are infectious proteins encoded by the host's DNA.

VIRAL GENETICS

- **Types of viral mutations**
 - ▶ **Spontaneous mutations:** Occur randomly with low rates among DNA viruses and generally higher rates in RNA viruses due primarily to high error rates in RNA-dependent RNA polymerases. Spontaneous mutants may acquire phenotypes that enable the virus to evade host immunity (eg, **antigenic drift** due to point mutations in influenza virus envelope proteins, hemagglutinin, and neuraminidase) or acquire antiviral drug resistance (eg, HIV).
 - ▶ **Induced mutations:** Generated in the laboratory to study viral gene function.

GENETIC INTERACTION BETWEEN DNA VIRUSES

- Homologous **recombination** (common among DNA viruses) between two strains of the same virus results in a hybrid virus with genes from both parents.

RECOMBINATION BETWEEN TWO VIRUS STRAINS



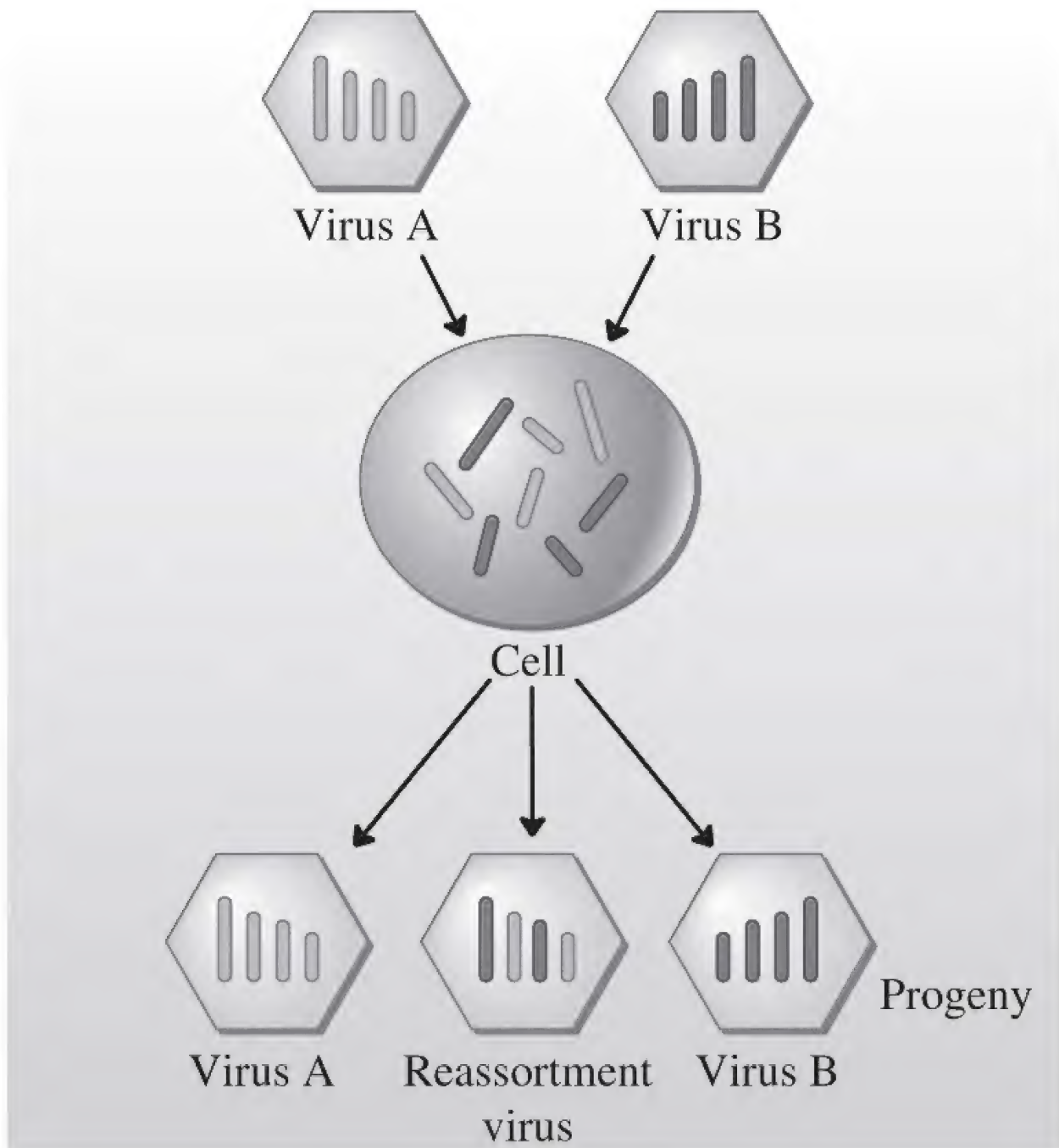
GENETIC INTERACTION BETWEEN RNA VIRUSES

- Random **reassortment** of gene segments is common in RNA viruses with segmented genomes (eg, influenza A virus).
- In a cell co-infected with two different viral strains, gene segments are exchanged and progeny viruses produced with RNA segments from either parental virus.
- Reassortment of RNA segments during infection of a cell with a human and animal influenza virus can result in major antigenic changes in the virus, termed **antigenic shift**.

GENE REASSORTMENT BETWEEN TWO SEGMENTED RNA VIRUSES

- **Complementation** is the interaction between viral proteins in a dually infected cell that results in increased production of one or both parental types.

- Complementation usually consists of one virus providing the functional gene product that is defective in the other virus.
- In complementation, viral proteins provide the missing or defective function, but the genotypes of parental and progeny viruses are unchanged.



VIRAL PATHOGENESIS

- Key concepts
 - ▶ Viral pathogenesis is a balance between virus offense and host defense.
 - ▶ Most virus infections are subclinical or inapparent.
 - ▶ **Virulence** is the capacity of a virus to cause disease.
 - ▶ Determinants of viral pathogenesis are entry into the host, mechanisms of virus spread, tissue tropism, effects of the virus on host cells, the host responses to virus infection, and virus evasion tactics.
- **Site of entry: Respiratory tract (most common), a alimentary/digestive tract, urogenital tract, skin, eyes, and conjunctiva.**
- **Many viruses transmitted via the bloodstream use an intermediate host or vector for transmission (eg, mosquito, tick).**
- **Mechanisms of virus spread**
 - ▶ Some virus infections remain **localized** to the site of entry after primary replication (eg, rhinovirus to respiratory tract, rotavirus to digestive tract, papillomavirus to skin).
 - ▶ **Systemic infection** is virus spread beyond the primary site of entry to multiple organs. Viruses spread systemically either via the bloodstream or the nervous system.

VIRAL PATHOGENESIS

- **Determinants of tissue tropism**
 - ▶ **Cell receptors:** Determine susceptibility of cells and tissues to virus infection.
 - ▶ **Virus receptors:** Viral proteins that mediate attachment to cell receptors.
 - ▶ **Other cellular proteins:** For example, cellular transcription factors and proteases are important determinants for permissive infections.
- **Host response to virus infection**
 - ▶ The nonspecific (innate) immune response is the front line of defense activated early in infection. Important players are interferon, natural killer cells, complement, and phagocytosis.
 - ▶ The specific (adaptive) immune response consists of acquired humoral and cell-mediated immunity essential for clearing the viral infection.

- **Virus immune evasion strategies**
 - ▶ **Antigenic variation** (eg, HIV, influenza virus).
 - ▶ **Establish an immunologically silent latent phase** (eg, herpesvirus).
 - ▶ **Hide in immunologically privileged sites** (eg, herpesviruses, papillomaviruses).
 - ▶ **Infect and suppress function of immune cells** (eg, HIV).
 - ▶ **Inhibit viral antigen presentation** (eg, adenoviruses and herpesviruses).
 - ▶ **Express extracellular immunomodulatory proteins** (eg, poxviruses and herpesviruses).
 - ▶ **Counteract the antiviral action of interferons** (eg, adenovirus, herpesviruses, HCV, influenza virus).

LABORATORY DIAGNOSIS OF VIRAL INFECTIONS

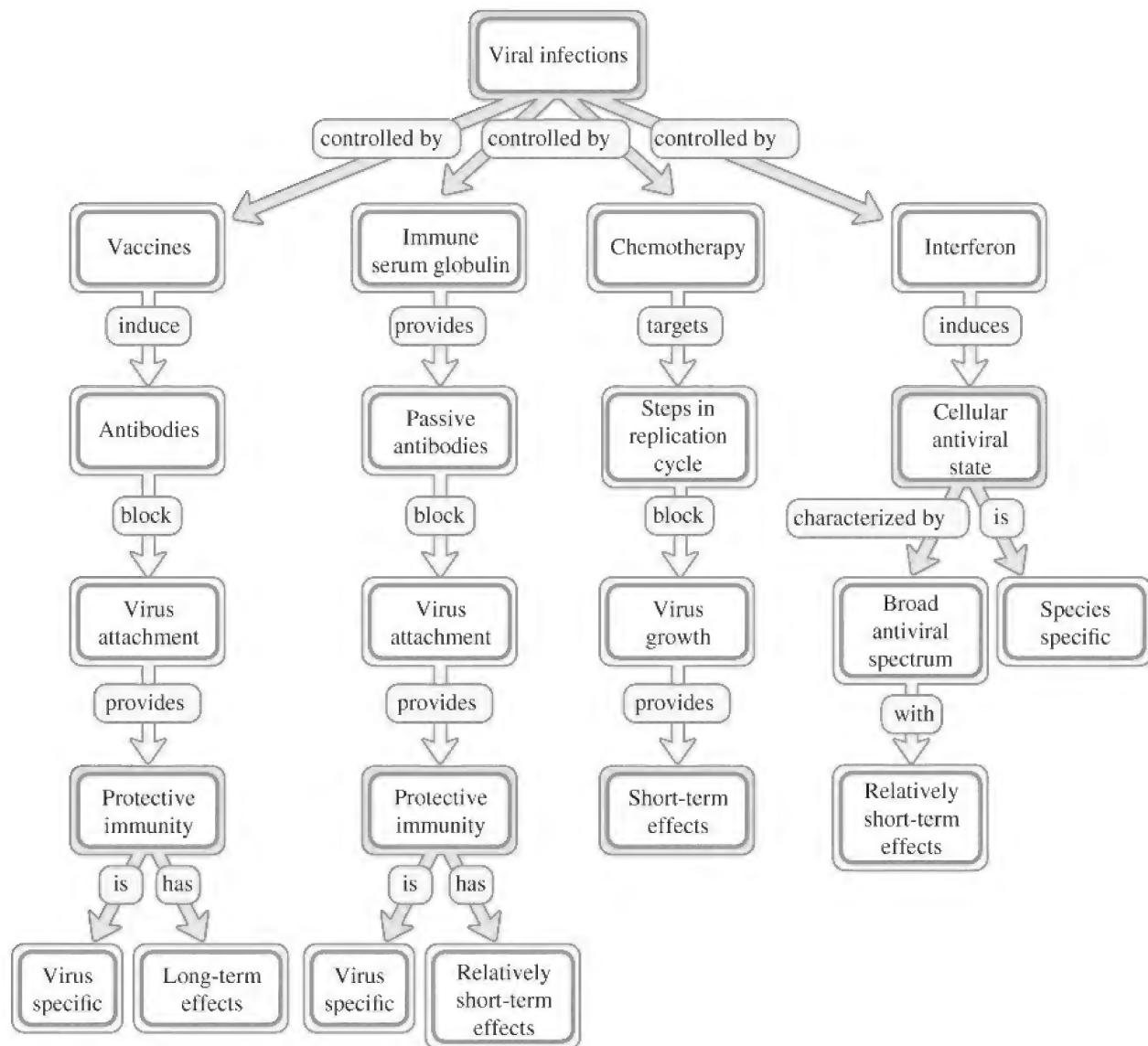
- **Nonculture methods**
 - ▶ **Cytology:** Inclusion bodies often typify specific viral infection (eg, intracytoplasmic **Negri bodies** are pathognomonic for **rabies virus**).
 - ▶ **Electron microscopy:** A rapid but insensitive method to detect viruses based on morphologic size and shape.
 - ▶ **Immunofluorescence and enzyme immunoassay (EIA) for viral antigen detection:** Both methods are sensitive and specific, rapid, and relatively inexpensive.
 - ▶ **Detection of viral nucleic acid:** PCR and nucleic acid hybridization are highly sensitive and specific methods to detect virus in clinical specimens. A variety of multiplex PCR-based nucleic acid detection assays are commercially available that can detect, for example, common respiratory or enteric viruses and their subtypes as etiologic agents. For example, a multiplex respiratory viral panel (RVP) may enable detection of influenza A and B, adenovirus, rhinovirus/enterovirus, RSV A and B, parainfluenza virus 1-3, coronavirus, and human metapneumovirus. The development and availability of multiplex assays are rapidly expanding diagnostic capabilities in the field of infectious diseases.
- **Cell culture methods**
 - ▶ **Cytopathic viruses** can be detected and presumptively identified by

characteristic cytopathic effect (CPE) produced when grown in cell cultures.

- ▶ **Noncytopathic viruses** do not produce CPE in cultured cells but viral antigen expression in cell culture can be detected by immunologic methods.
- **Serologic methods**
 - ▶ **Detection of antiviral antibody:** Serology to detect a rise in antibody titer to a specific virus during the acute and convalescent phase of infection provides a retrospective diagnosis of a recent virus infection. Detection of virus-specific IgM or IgG antibody by serology is a common method of viral diagnosis.

ANTIVIRAL THERAPY

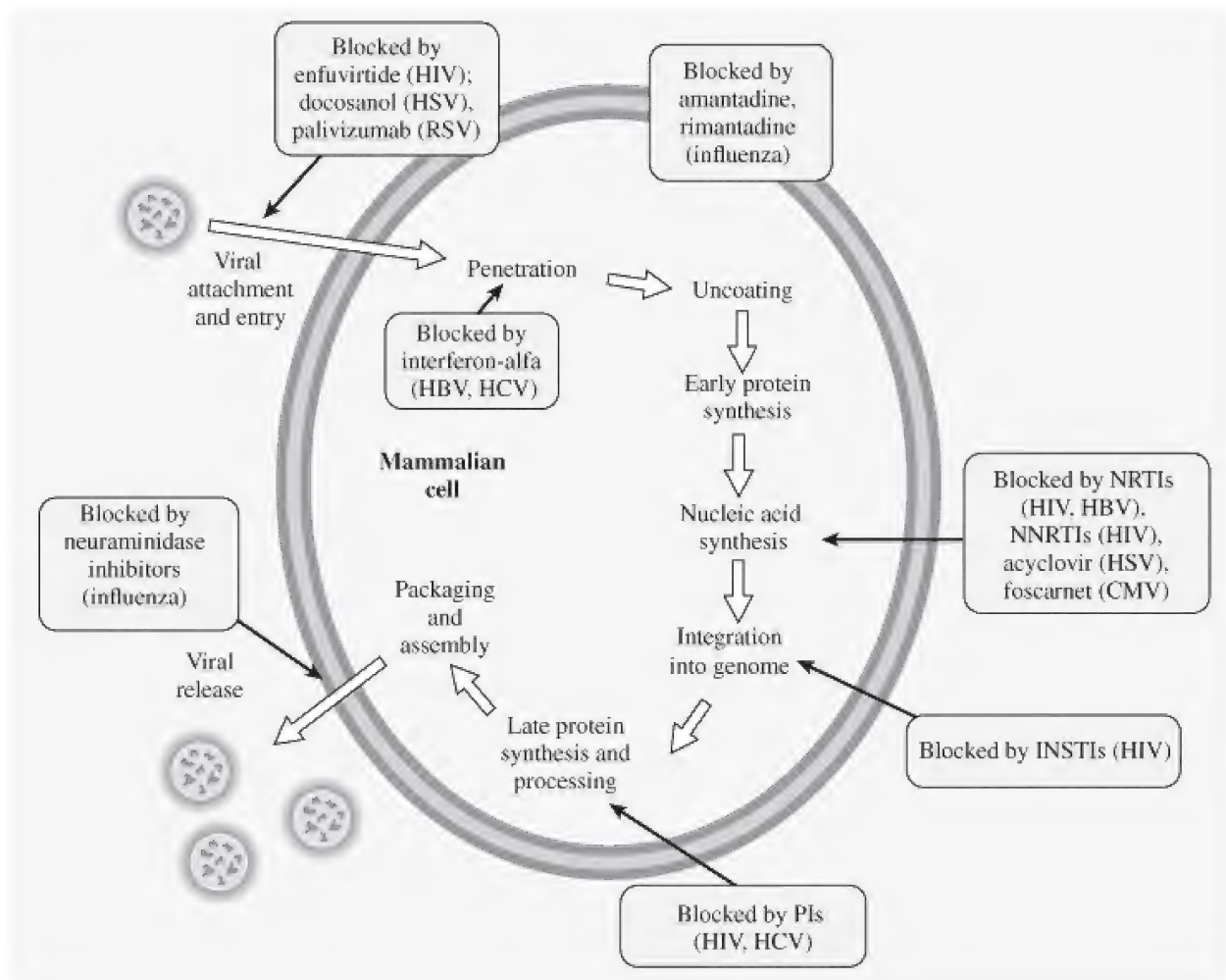
Control of Viral Infections



ANTIVIRAL THERAPY

- **Antiviral drug targets**

- ▶ Viruses have complex life cycles that are susceptible to attack by drugs at several stages.



Reproduced, with permission, from Katzung BG, and Trevor AJ. *Basic & Clinical Pharmacology*. 13th ed. New York: McGraw-Hill; 2015.

Major sites of antiviral drug action. Note: Interferon alphas are speculated to have multiple sites of action. NRTIs, nucleoside reverse transcriptase inhibitors; NNRTIs, nonnucleoside RTIs; INSTIs, integrase strand transfer inhibitors; PIs, protease inhibitors.

- **Antiviral therapies that block attachment or entry**

- ▶ Antiviral antibody and receptor analogues or decoys **block attachment of the virus to the cell receptor** (eg, ICAM-1 receptor for rhinoviruses, CD4 or CCR5 receptor for HIV).
- ▶ **Amantadine** and **rimantadine** block penetration and uncoating of influenza A virus by inhibiting fusion of the viral envelope with the endosomal membrane.
- ▶ Enfuvirtide (T-20) blocks HIV-1 entry by inhibiting fusion of HIV-1 with

CD4+ cells.

- ▶ Maraviroc blocks binding of HIV to the CCR-5 chemokine co-receptor on target cells.
- ▶ Palivizumab, monoclonal antibody against the surface F glycoprotein of RSV. Approved for prevention of serious lower respiratory tract disease in high-risk pediatric patients.
- ▶ Docosanol (topical) blocks entry of HSV by inhibiting fusion of viral envelope with host cell.

ANTIVIRAL THERAPY

- **Antiviral drugs that inhibit viral nucleic acid synthesis**
 - ▶ **Nucleoside analogue inhibitors of herpesvirus family: acyclovir, valacyclovir, famciclovir**
 - Valacyclovir and famciclovir are prodrugs (precursor forms) with improved oral bioavailability relative to acyclovir.
 - All three drugs are selectively phosphorylated in herpesvirus-infected cells by viral-encoded thymidine kinase to inhibit viral DNA polymerase and cause viral DNA chain termination.
 - Approved to treat most HSV and VZV infections.
 - ▶ **Nucleoside analogue inhibitors of herpesvirus family: ganciclovir and valganciclovir**
 - Valganciclovir is the prodrug of ganciclovir with greater oral bioavailability.
 - Approved to treat CMV disease and CMV retinitis.
 - Drugs are preferentially phosphorylated by CMV-encoded protein kinase to inhibit viral DNA polymerase and cause viral DNA chain termination.
 - ▶ **Nonnucleoside analogue inhibitor of herpesvirus family: foscarnet**
 - Foscarnet does not require intracellular metabolism for activation.
 - Foscarnet is a pyrophosphate analogue that binds directly to the pyrophosphate binding site of DNA polymerase to inhibit viral DNA polymerase.
 - It has a broad spectrum of activity against herpesviruses and activity against HIV. Clinically, foscarnet is used to treat infections due to

CMV (particularly when ganciclovir cannot be used) and acyclovir-resistant HSV or VZV. Foscarnet is not used to treat HIV.

ANTIVIRAL THERAPY

- **Antiviral drugs that inhibit viral nucleic acid synthesis**
 - ▶ **Nucleotide analogue inhibitor of CMV: cidofovir**
 - It does not require viral kinases to be converted to an active form.
 - It is converted by cellular kinases to its active diphosphorylated form, which acts as a competitive inhibitor of viral DNA polymerase.
 - It is used for treatment of CMV retinitis in patients with HIV/AIDS, and has been used for treatment of acyclovir- and foscarnet-resistant HSV or CMV infections.
 - ▶ **Nucleoside analogue reverse transcriptase inhibitors (NRTIs) of retroviruses: abacavir, didanosine, emtricitabine, lamivudine, tenofovir, zidovudine.**
 - All are competitive inhibitors of HIV RT and chain terminators of viral DNA synthesis.
 - These drugs are used to treat HIV infections in combination with other antiretroviral drugs.

ANTIVIRAL THERAPY

- **Antiviral drugs that inhibit viral nucleic acid synthesis**
 - ▶ **Nonnucleoside reverse transcriptase inhibitors (NNRTIs): delavirdine, efavirenz, etravirine, nevirapine, rilpivirine**
 - These drugs bind to specific sites on HIV RT that are different from the substrate-binding site.
 - They are used to treat HIV infections in combination with other antiretroviral drugs.
 - ▶ **Integrase strand transfer inhibitors (INSTIs): dolutegravir, elvitegravir, raltegravir**
 - Selectively inhibit HIV integrase function by preventing integration of viral DNA and inhibiting HIV replication.

- Used in combination antiretroviral therapy.
- ▶ **Inhibitors of other viruses: ribavirin, adefovir, entecavir**
 - Ribavirin is phosphorylated by cellular kinases and incorporated into newly synthesized viral genomes by viral RNA-dependent RNA polymerase.
 - Ribavirin exerts its antiviral effect by lethally mutating the viral RNA genome.
 - In an alternate mechanism, ribavirin acts by inhibiting the synthesis of guanosine triphosphate (GTP), resulting in depleted GTP pools required for viral transcription and replication.
 - Ribavirin is used in combination with interferon-alpha to treat chronic hepatitis C infection, but more recently has been supplanted by DAAs (see below).
 - Ribavirin has been used to treat hemorrhagic fever viruses (eg, Lassa fever virus) and RSV.
 - Entecavir is a guanosine nucleoside analogue with marked activity against HBV DNA polymerase.

Direct-acting agents (DAAs) : Inhibit hepatitis C virus (HCV). There are currently four major classes of DAAs that are used in **combination therapy**. The four classes are determined by their mechanism of action and therapeutic target: (1) nonstructural proteins 3/4A (NS3/4A) protease inhibitors (PIs), (2) NS5B nucleotide polymerase inhibitors (NPIs), (3) NS5B nonnucleoside polymerase inhibitors (NNPIs), and (4) NS5A inhibitors. Examples from each class include the following:

Simeprevir, grazoprevir, or paritaprevir blocks HCV NS3/4A protease responsible for viral protein processing and evasion of host immune response.

Sofosbuvir, a nucleotide polymerase inhibitor (NPI), that blocks HCV NS5B RNA-dependent RNA polymerase, necessary for viral RNA synthesis.

Dasabuvir, a nonnucleoside polymerase inhibitor (NNPI), that blocks HCV NS5B RNA-dependent RNA polymerase.

Ledipasvir, elbasvir, ombitasvir, daclatasvir, or velpatasvir inhibit HCV NS5A, a viral phosphoprotein involved in viral replication, assembly, secretion, and spread.

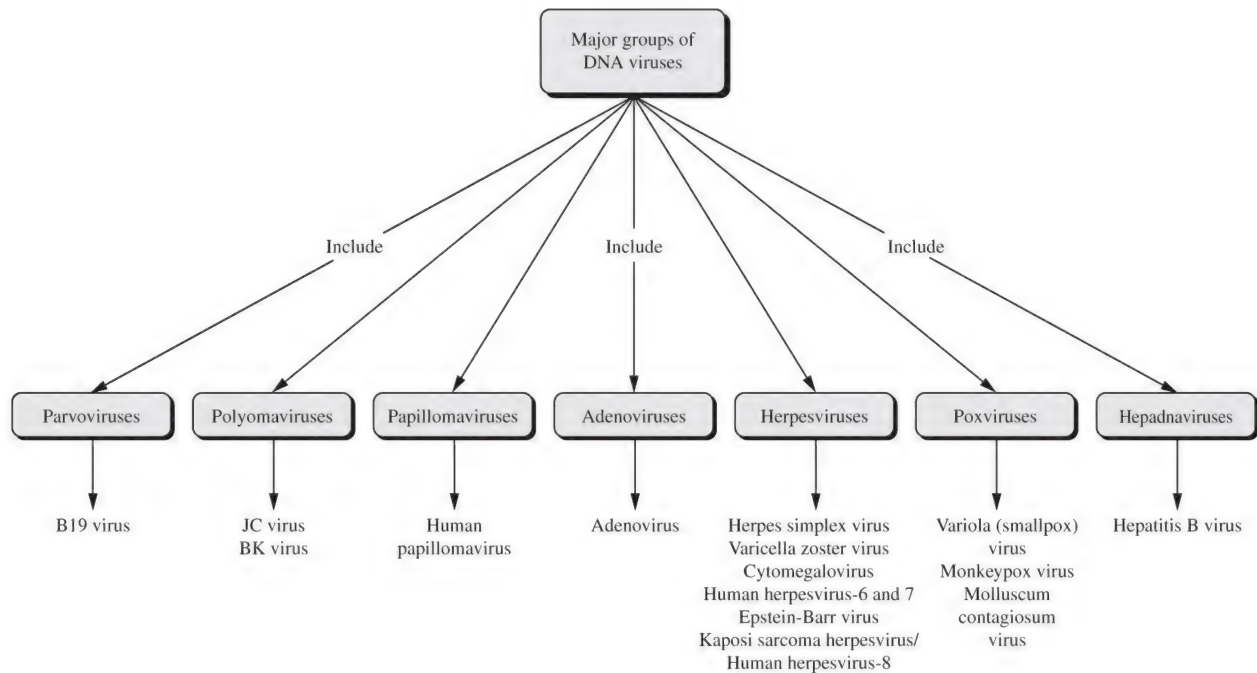
The DAAs have revolutionized the treatment and cure of chronic HCV.

ANTIVIRAL THERAPY

- **Antiviral drugs that inhibit HIV protease: atazanavir, atazanavir-cobicistat, darunavir, darunavir-cobicistat, fosamprenavir, indinavir, lopinavir/ritonavir, saquinavir, tipranavir.**
 - Protease inhibitors bind to the active site of HIV-1 protease to inhibit its action.
 - A combination of protease inhibitors plus nucleoside and nonnucleoside RT inhibitors is the standard therapy for HIV-1 infection.
- **Interferons (IFNs).** IFNs are host cell proteins with significant antiviral and immunomodulatory effects.
 - IFN-alpha and IFN-beta are two major types of IFN.
 - Antiviral activity induced by IFN results in the activation of enzyme activity that inhibits viral protein synthesis.
 - Recombinant IFN-alpha can be beneficial in treatment of chronic hepatitis B infection.

ANTIVIRAL THERAPY

- **Antiviral drugs that inhibit virus release**
 - **Neuraminidase inhibitors (zanamivir, oseltamivir, and peramivir)** are selective inhibitors of influenza virus neuraminidase.
 - Neuraminidase inhibitors are sialic acid analogues that block the active site of the viral neuraminidase responsible for cleaving sialic acid on the cell surface and releasing the virus.
 - These drugs block release of influenza virus from infected cells and reduce virus spread to adjacent cells.
 - They are active against both influenza A and B viruses and are used for treatment of influenza A and B virus infections.



KEY CONCEPTS

- Most DNA viruses have double-stranded (ds) DNA genomes; the one human virus exception is the Parvoviridae family, whose members have a single-stranded DNA genome.
- All DNA viruses, except poxviruses, have icosahedral nucleocapsid symmetry; poxviruses have complex symmetry.
- Medically important DNA viruses comprise seven virus families (Parvoviridae, Polyomaviridae, Papillomaviridae, Adenoviridae, Herpesviridae, Poxviridae, and Hepadnaviridae) and share similar properties.

PROPERTIES OF DNA VIRUSES

Virus Family	DNA Structure	Shape	Envelope	Virion Polymerase	Site of Replication	Human Viruses
Parvoviridae	Ss linear	Icosahedral	No	No	Nucleus	B19 virus
Polyomaviridae	Ds circular	Icosahedral	No	No	Nucleus	JC & BK virus
Papillomaviridae	Ds circular	Icosahedral	No	No	Nucleus	Papillomavirus
Adenoviridae	Ds linear	Icosahedral	No	No	Nucleus	Adenovirus
Herpesviridae	Ds linear	Icosahedral	Yes	No	Nucleus	HSV, CMV, EBV, VZV, HHV-6, HHV-8
Poxviridae	Ds linear	Complex	Yes	Yes	Cytoplasm	Variola major, Molluscum contagiosum
Hepadnaviridae	Partial Ds circular	Icosahedral	Yes	Yes	Nucleus	Hepatitis B virus

Several children in a kindergarten class were seen at a pediatric practice with a bright red rash on the cheeks. All children were in good physical condition, none had fever or other symptoms and some had an abdominal rash. The rashes resolved over 1 to 2 weeks without specific treatment.

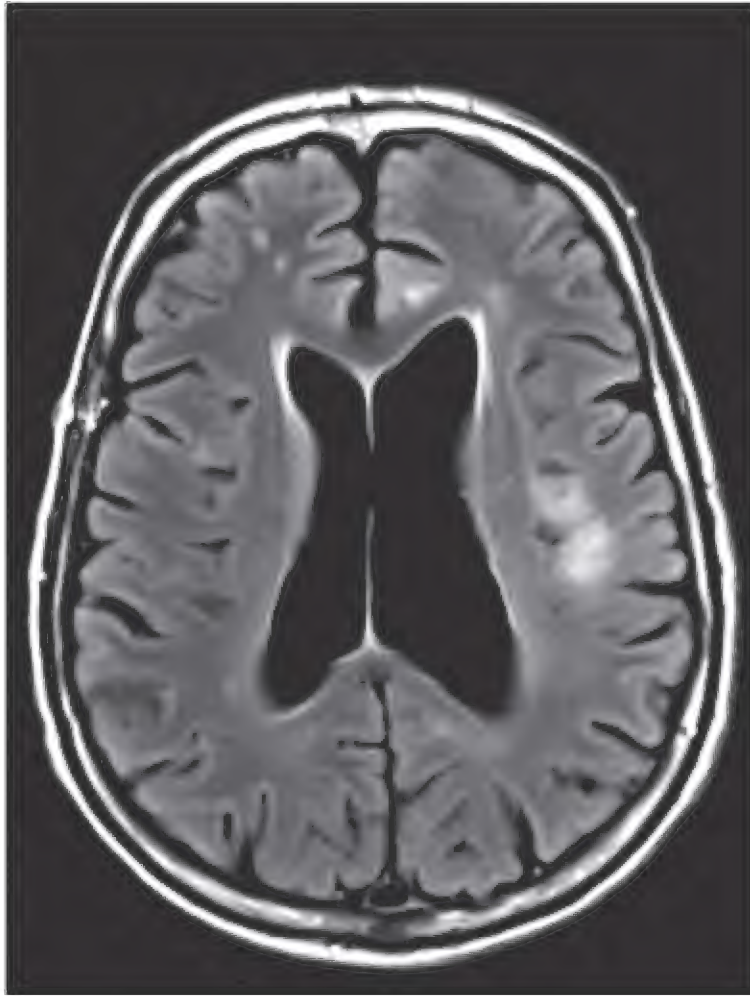


Source: Centers for Disease Control and Prevention, Washington, DC.

Erythema Infectiosum (Fifth Disease)

Etiology and Epidemiology	Caused by parvovirus B19 . Transmitted by the respiratory route; high transmission rates among household contacts. B 19 infections occur worldwide with seroconversion rates greater than 50% in adults.
Clinical Manifestations	<p>Childhood rash characterized by generalized erythema and a rash of the face, giving a “slapped cheek” appearance. Usually presents as a mild systemic illness followed a week or two later by the characteristic rash and then resolves over the course of a few weeks.</p> <p>Parvovirus B19 infection can cause arthralgia and arthritis in adults and aplastic crisis in patients with hemolytic anemia or sickle cell disease.</p> <p>Infection of pregnant women can lead to fetal anemia and death or generalized fetal anemia and congestive heart failure (hydrops fetalis).</p>
Pathogenesis	<p>Parvovirus B19 infects erythroid precursors in bone marrow and replicates preferentially in proliferating hematopoietic cells. It is cytolytic to immature erythroid cells, resulting in suppression of erythropoiesis and anemia.</p> <p>In immunocompetent persons, recovery is associated with an antibody response that clears the virus and confers long-term protection.</p>
Laboratory Diagnosis	Detection of parvovirus B19-specific IgM antibody or PCR detection of viral DNA.
Treatment and Prevention	No specific treatment or vaccine is available for parvovirus B 19.

A 69-year-old man with complaints of speech and vision abnormalities and decreasing mental function is referred to a neurologist. The patient has a 3-year history of chronic lymphocytic leukemia that is being treated with chemotherapy. MRI reveals multiple focal areas of demyelination.

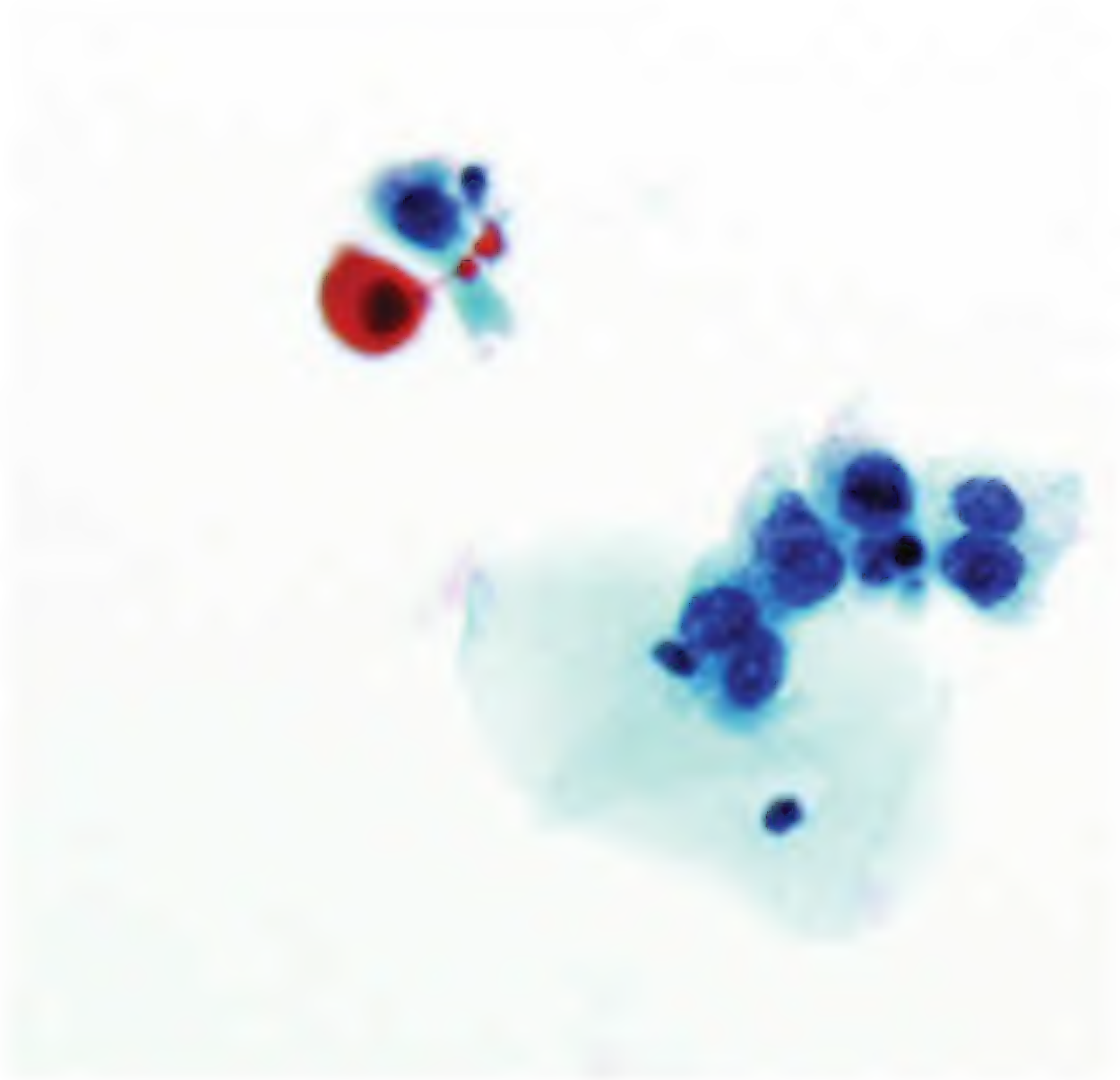


MRI of the brain shows multifocal areas of demyelination seen as areas of increased signal appearing white against the darker background. (Reproduced, with permission, from Ropper AH, Samuels MA, Klein J, eds. *Adams and Victor's Principles of Neurology*. 10th ed. New York: McGraw-Hill; 2014.)

Progressive Multifocal Leukoencephalopathy (PML)

Etiology and Epidemiology	<p>PML is caused by a human polyomavirus, JC virus (JCV). JCV is transmitted by respiratory tract droplets and causes a widespread asymptomatic childhood illness with 70%–80% of adults seropositive to JCV.</p> <p>JCV causes an opportunistic infection of the brain in immunocompromised individuals, such as in the elderly with immunodeficiency states, patients undergoing immunosuppressive therapy for organ transplantation or chemotherapy for cancer, and patients with HIV/AIDS.</p>
Clinical Manifestations	<p>PML is a demyelinating disease of the brain in adults with immunosuppressive diseases. Onset is insidious, with early signs of speech and vision abnormalities and altered mental status. The clinical course is progressive, culminating in coma and death within 6 months of onset.</p>
Pathogenesis	<p>JCV is acquired by the respiratory route and spread by viremia to establish latent infection in multiple organs. In immunosuppressed individuals, JCV is activated, spreads to the brain, and causes lytic destruction of oligodendrocytes, the major myelin-producing cells in the CNS.</p>
Laboratory Diagnosis	<p>JCV is detected by PCR in cerebral spinal fluid of patients with PML. JCV is also detected in brain biopsy specimens by PCR or in situ DNA hybridization.</p>
Treatment and Prevention	<p>No specific treatment or vaccine is available for JCV infection.</p>
Notes	<p>PML is an AIDS-defining illness.</p>

A 25-year-old woman presents to her gynecologist with complaints of itching, burning, and tenderness in the genital area. The patient is sexually active but with no history of sexually transmitted disease. Physical examination is significant for flesh-colored exophytic papules on the labia and vulva. A Pap smear is performed to check for cervical abnormalities.

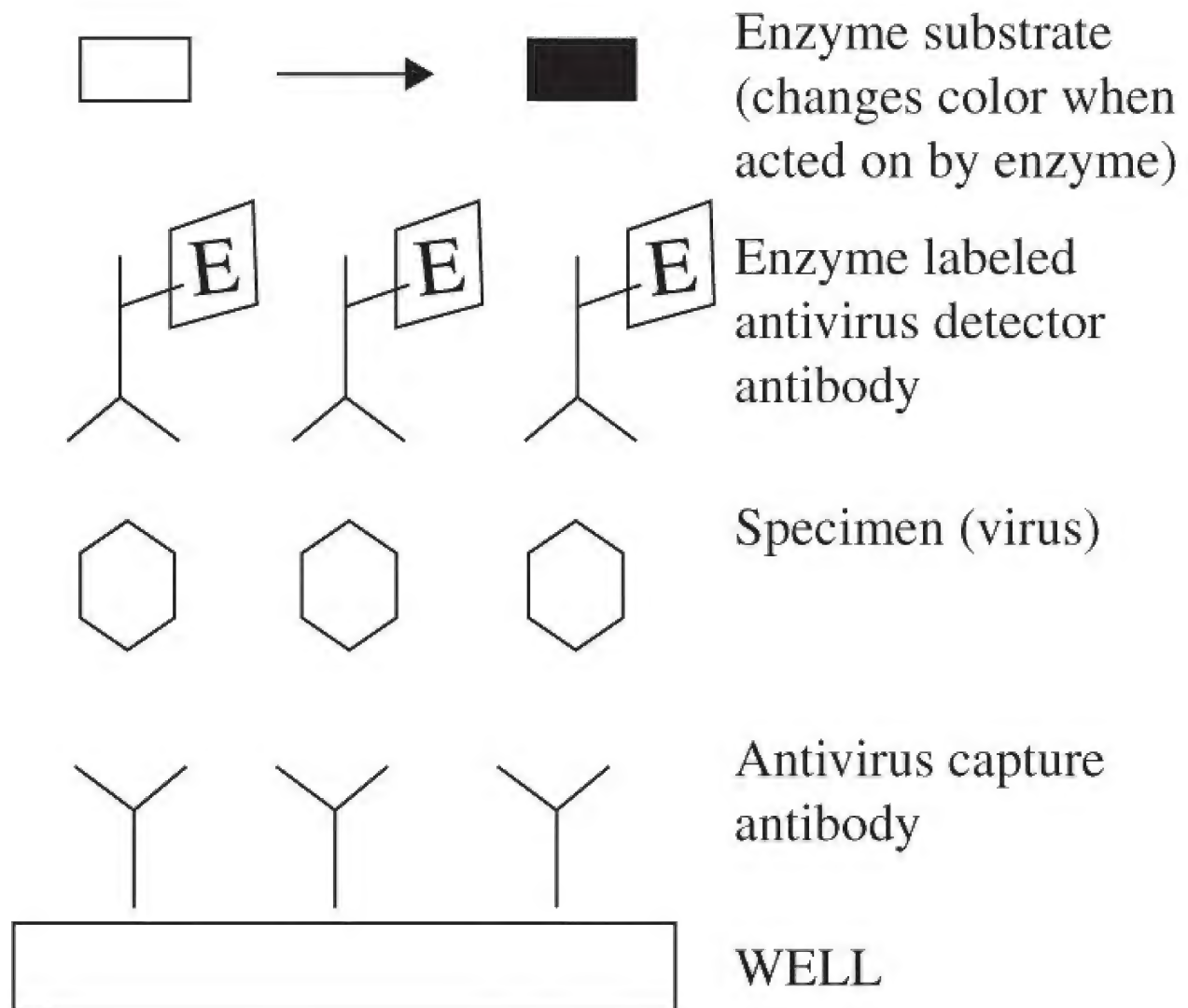


Abnormal Pap smear. Dysplastic squamous cells have nuclear membrane irregularities and increased nuclear to cytoplasmic size ratio. (Reproduced, with permission, from Hoffman BL et al. *Williams Gynecology* . 3rd ed. New York: McGraw-Hill; 2016.)

Genital Warts (Condyloma acuminata)

Etiology and Epidemiology	Caused by human papillomavirus (HPV) , most commonly HPV types 6 and 11. Transmitted sexually. More than 100 different genotypes of HPV identified and divided into low-risk and high-risk oncogenic types . Low-risk types (HPV 6 and 11) cause benign genital warts; high-risk types (HPV 16 and 18) are tightly linked with cervical cancer.
Clinical Manifestations	External genital warts are associated with benign HPV 6 and 11. HPV types 1, 2, and 4 cause common warts of the hands and feet . HPV 6 and 11 cause benign laryngeal papillomas in children infected in the birth canal of a mother with genital warts. Oncogenic HPV 16 and 18 are associated with anogenital cancer and oropharyngeal cancer .
Pathogenesis	HPV targets basal epithelial cells and gains entry through cracks in skin or tears or lacerations in mucosal surfaces during sexual intercourse. Infection remains localized and may resolve spontaneously, remain latent, or (depending on HPV type) progress to dysplasia and carcinoma. HPV infections are eradicated and controlled by cell-mediated immunity.
Laboratory Diagnosis	Condyloma acuminata is diagnosed clinically. Cervical cytology evaluated by the Papanicolaou (Pap) smear is the gold standard in cervical cancer diagnosis. PCR or DNA hybridization with HPV type-specific probes is used to distinguish low-risk and high-risk oncogenic types.
Treatment and Prevention	Warts are treated surgically (cryotherapy, laser therapy) or topically with chemical agents (podophyllin, trichloroacetic acid) to remove the warts. Imiquimod, an inducer of interferon and other cytokines, is used topically to treat genital warts. HPV vaccination is recommended for girls and boys at age 11 or 12 years old. Recombinant quadrivalent HPV vaccines are available that protect against HPV 16 and 18 (responsible for ~70% of cervical cancer) and HPV 6 and 11 (responsible for 90% of genital warts). A 9-valent HPV vaccine (Gardasil 9) is available that covers five additional HPV types (31, 33, 45, 52, 58) responsible for 20% of cervical cancer.

A 9-year-old girl is seen in a pediatric practice with conjunctivitis and a sore throat that has continued for 3 days. On examination, the child has a fever; pharyngitis; conjunctival redness, watering, and pain; and cervical adenopathy. A rapid strep test is negative. Conjunctival and pharyngeal swab specimens are obtained for viral culture and antigen detection. The patient is sent home with symptomatic treatment.



Enzyme immunoassay (EIA) for detection of viral antigen.

Adenovirus Pharyngoconjunctival Fever

Etiology and Epidemiology	Pharyngoconjunctival fever is caused by adenoviruses , primarily types 3 and 7, and is more prevalent in children. About 50 different adenovirus serotypes are known. Adenoviruses are transmitted by the respiratory route, by the fecal-oral route , or through direct inoculation of the eyes by fingers.
Clinical Manifestations	<p>Pharyngoconjunctival fever (adenovirus types 3 and 7) is characterized by fever, pharyngitis, conjunctivitis, and cervical adenopathy.</p> <p>Adenoviruses are also responsible for:</p> <ul style="list-style-type: none"> • Pharyngitis and coryza • Tonsillitis in young children • Acute respiratory disease (ARD) (adenovirus types 4 and 7) primarily in military recruits • Keratoconjunctivitis (adenovirus types 8, 19, and 37) usually in adults • Acute gastroenteritis (adenovirus types 40 and 41) in infants and young children • Hemorrhagic cystitis (adenovirus type 11) • Severe respiratory illness/pneumonia (adenovirus type 14) in patients of all ages
Pathogenesis	Adenoviruses infect epithelial cells of the respiratory tract and intestinal tract and cause direct cytotoxic damage. Infection is cleared by cell-mediated immunity; type-specific antibody provides long-term protection.
Laboratory Diagnosis	Adenovirus infections are detected by isolation and identification in cell culture, direct antigen detection in clinical specimens, PCR, and serology.
Treatment and Prevention	There is no specific antiviral therapy or vaccine available for adenovirus infection. Handwashing is effective in preventing adenovirus infections.

A 20-year-old woman presents to the university health clinic with painful vesicular lesions on the vulva and perineum. She has not felt well the past week and complains of pain on urination. While taking the history, you find that she has had unprotected sex with a new partner during the past month. On physical examination, she has a low-grade fever and inguinal lymphadenopathy. You swab a vesicular lesion and submit the specimen to the laboratory to confirm your diagnosis.



Vesicles, ulcers and erythema in primary vulvar infection. (Reproduced, with permission, from Wolff K, Johnson RA, Suurmond D. *Fitzpatrick's Color Atlas and Synopsis of Clinical Dermatology*. 5th ed. New York: McGraw-Hill; 2005.)

Genital Herpes

Etiology and Epidemiology	Genital herpes is caused by herpes simplex type 2 (HSV-2) with about 20% of cases caused by HSV-1. HSV-1 and HSV-2 are transmitted by direct contact with virus-containing secretions/body fluids such as saliva and genital secretions during sexual contact. Risk factors include unprotected sexual intercourse, multiple sex partners, having sex early (before 17 years of age), and a history of STIs. Infected individuals can shed infectious virus in the absence of clinical symptoms and in the absence of visible lesions.
Clinical Manifestations	Genital herpes presents as painful vesicular lesions of the penis, cervix, vulva, vagina, or perineum accompanied by fever, dysuria, localized lymphadenopathy, and malaise lasting 1–2 weeks.
Pathogenesis	HSV causes localized infection of mucosal epithelial cells. Virus spreads to innervating neurons and is transported to dorsal root ganglia to establish latent infection. Reactivation of latency is triggered by external factors (eg, fever, sunlight, stress, immune suppression) that induce transport down the axon with infection of epithelial cells innervated by the sensory nerve. Reactivation results in recurrent vesicular lesions.
Laboratory Diagnosis	Tzanck smear of cells from the lesion detects multinucleated giant cells. HSV can be detected by culture or identified by PCR assay or with HSV type-specific fluorescent antibody staining.
Treatment and Prevention	HSV infections are treated with acyclovir or the prodrugs, valacyclovir or famciclovir. Barrier contraceptives and safe sex are preventive measures.

Notes

A 55-year-old woman undergoing chemotherapy for metastatic breast cancer is seen by her oncologist because of itchy, burning blisters on her rib cage that began 3 days earlier as a tingly or numb sensation. Physical examination reveals an uncomfortable-appearing patient with vesicular eruptions along a distinct thoracic dermatome that do not cross midline.



Vesicles along dermatome of a thoracic nerve.

Herpes Zoster (Shingles)

Etiology and Epidemiology	Shingles is caused by the herpesvirus, varicella-zoster virus (VZV) . Primary infection by VZV causes varicella (chickenpox), usually in children, which reactivates as zoster (shingles) in adults. VZV is transmitted by respiratory droplets and is highly contagious. Herpes zoster occurs only in persons with a previous primary varicella-chickenpox infection.
Clinical Manifestations	Primary VZV infection is characterized by fever and malaise and then a generalized vesicular rash that progresses to pustules and scabs (chickenpox). Reactivation of latent VZV results in herpes zoster (shingles) characterized by painful vesicular lesions in the skin along a dermatome innervated by a particular sensory ganglion. Postherpetic neuralgia is a common complication of herpes zoster that may persist for years.
Pathogenesis	VZV initially infects respiratory epithelial cells, then spreads via lymphatics and blood to skin where a vesicular rash occurs; virus spreads to innervating neurons and establishes latent infection in dorsal root ganglia. Reactivation of latency is triggered by increasing age, immunocompromised status due to cancer, chemotherapy, HIV/AIDS, or immunosuppressive therapy for organ transplantation or other conditions. Humoral immunity is important in preventing respiratory infection; cell-mediated immunity is important for clearing primary and recurrent VZV infections.
Laboratory Diagnosis	Varicella or zoster is usually diagnosed clinically. Tzanck smear of cells from a lesion detects multinucleated giant cells. VZV can be detected by culture and identified by PCR assay or with VZV-specific antibody staining.
Treatment and Prevention	VZV infections are treated with acyclovir or prodrugs, valacyclovir or famciclovir. Live, attenuated VZV vaccines are available to prevent varicella in children (Varivax) and shingles (Zostavax) in adults older than 60 years and who have had varicella. Passive administration of VZV immune globulin is used to prevent disease in immunocompromised patients exposed to VZV.

A 55-year-old recipient of a kidney transplant is seen by a nephrologist with complaints of fever, fatigue, malaise, and myalgias for the past week. Since the organ transplant 4 months ago, the patient has received cyclosporine, azathioprine, and prednisone as maintenance immunosuppressive therapy. Lab findings of significance are leukopenia, thrombocytopenia, and elevated liver enzymes. A blood specimen is submitted for detection of viral antigen and DNA.

Cytomegalovirus (CMV) Disease

Etiology and Epidemiology	CMV causes opportunistic infections in organ transplant recipients. CMV is transmitted by direct contact with bodily fluids (blood, saliva, semen, cervical secretions, breast milk). CMV is ubiquitous and persists indefinitely after primary infection as a latent infection in mononuclear cells.
Clinical Manifestations	<p>CMV causes a mononucleosis-like syndrome clinically similar to EBV in immunocompetent children and adults. CMV disease is a common cause of morbidity and mortality in transplant recipients and increases the risk of graft failure. CMV is a common opportunistic pathogen in patients with HIV/AIDS and can cause retinitis, encephalitis, and colitis.</p> <p>Congenital CMV infection causes cytomegalic inclusion disease characterized by hepatosplenomegaly, jaundice, petechiae, microcephaly, growth retardation, and neurologic complications.</p>
Pathogenesis	CMV initiates infection in the oropharynx, spreads to lymphatic tissue, and produces viremia that disseminates virus to multiple organs (liver, spleen, kidney, lungs). CMV remains latent in mononuclear cells and is reactivated in immunosuppressed patients. CMV infections are controlled by cell-mediated immunity.
Laboratory Diagnosis	CMV is detected by cell culture isolation and identification with CMV-specific antibody, antigenemia in leukocytes from blood, and PCR to detect viral load.
Treatment and Prevention	Ganciclovir or the prodrug, valganciclovir, is the antiviral drug of choice to treat CMV infection. Foscarnet is used for ganciclovir-resistant infections. No vaccine is available to prevent CMV infections.
Notes	

A 9-month-old infant is seen in a pediatric practice with a history of irritability and a fever of 39.5°C for 3 days followed by the appearance of a generalized erythematous maculopapular rash on the neck and trunk. The infant was treated symptomatically and recovered within a few days without complications.

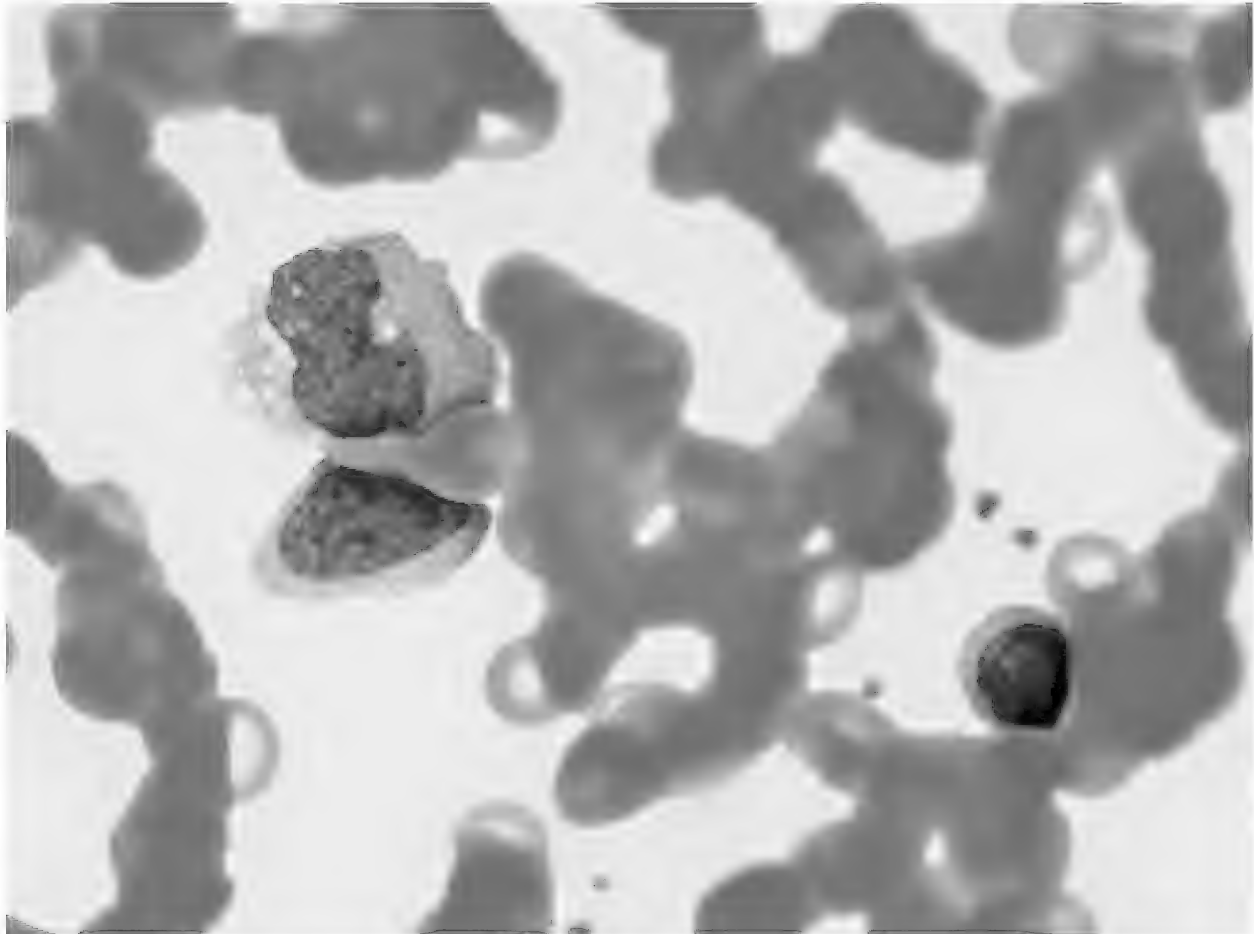


Toddler with maculopapular skin rash. (Reproduced, with permission, from Wolff K, Johnson RA,

Exanthem subitum (Roseola)

Etiology and Epidemiology	Exanthem subitum (roseola) is caused by human herpesvirus 6 (HHV-6); human herpesvirus 7 (HHV-7) is responsible for about 10% of roseola cases. HHV-6 and HHV-7 are acquired during infancy and transmitted by saliva ; 60%–90% of adults are seropositive for viral antibody.
Clinical Manifestations	The disease is characterized by high fever for 2–5 days followed by the appearance of a rash spreading from the trunk to the extremities. More severe forms can result in febrile seizures with or without rash. Reactivation of latent HHV-6 or HHV-7 can occur in immunocompromised individuals (transplant recipients, patient with HIV/AIDS) and is associated with pneumonitis, encephalitis, hepatitis, or graft rejection.
Pathogenesis	HHV-6 and HHV-7 infect and establish latent infection of T lymphocytes. Virus is reactivated in immunocompromised individuals. HHV-6 may be a cofactor in the pathogenesis of HIV/AIDS.
Laboratory Diagnosis	HHV-6 and HHV-7 are detected by PCR and serological assays.
Treatment and Prevention	No specific antiviral therapy or vaccines are available for HHV-6 or HHV-7 infections.
Notes	

A 19-year-old college student presents to the student health clinic complaining of fever, fatigue, and sore throat that developed about a month after spring break. Physical examination shows pharyngitis, cervical and axillary lymphadenopathy, and splenomegaly. Laboratory tests show atypical lymphocytes and are positive for heterophile antibody.



Atypical lymphocytes seen in blood smear. Note 2 atypical lymphocytes (enlarged nucleus and abundant cytoplasm, left side, and normal lymphocyte, right side). (Reproduced, with permission, from Kasper et al, eds. *Harrison's Principles of Internal Medicine* . 19th ed. New York: McGraw-Hill; 2015.)

Infectious Mononucleosis

Etiology and Epidemiology	Epstein-Barr virus (EBV) is the most common cause of infectious mononucleosis in young adults. EBV is distributed worldwide and transmitted by saliva .
Clinical Manifestations	Infectious mononucleosis is characterized by fever, pharyngitis, fatigue, headache, malaise, lymphadenopathy, splenomegaly, and elevated liver enzymes. Symptoms are usually self-limited, but fatigue may persist for months. EBV is associated with lymphoproliferative disorders and is closely linked with Burkitt's lymphoma , nasopharyngeal carcinoma , and Hodgkin's disease .
Pathogenesis	EBV initiates infection of oropharyngeal cells and spreads to infiltrating B lymphocytes, causing a latent infection that persists for life. EBV stimulates B-cell mitogenesis and immortalizes B cells. Cytotoxic T cells control B-cell outgrowth. Latent infection and immortalization of a small proportion of B cells may result in EBV-associated tumors years later. EBV DNA and proteins are commonly found in EBV-associated tumors.
Laboratory Diagnosis	EBV mononucleosis is diagnosed by the demonstration of atypical lymphocytes (Downey cells) in a blood smear. A heterophile antibody -positive test result (Monospot test) is diagnostic for EBV infectious mononucleosis. EBV-specific serologic tests or PCR assay can be used to diagnose EBV infection.
Treatment and Prevention	There is no specific antiviral therapy for EBV or vaccine to prevent EBV infection.
Notes	

A 28-year-old homosexual man is seen by a dermatologist with complaints of bluish-purple spots on his chest, thigh, and foot. The patient's medical history is significant for feeling tired with intermittent diarrhea for the past year. He reports having had unprotected sex with multiple partners over the past few years. Physical examination revealed generalized lymphadenopathy. A biopsy of a lesion is obtained and submitted to confirm the diagnosis.



Dark purple lesions on foot. (Source: Centers for Disease Control and Prevention, Washington, DC.)

Kaposi Sarcoma

Etiology and Epidemiology	Kaposi sarcoma herpesvirus (KSHV)/human herpesvirus type 8 (HHV-8) causes epidemic Kaposi sarcoma (KS) primarily in patients with HIV/AIDS. KSHV is transmitted by saliva and semen .
Clinical Manifestations	KS is a spindle-cell tumor of endothelial cell origin characterized by lesions on the skin, face, or oral cavity that appear as bruised or discolored spots that progress to ulcerated nodules. KSHV also causes primary effusion lymphoma , an AIDS-associated B-cell lymphoma in body cavities, and multicentric Castleman disease , a multicentric angiofollicular B-cell lymphoproliferative disorder.
Pathogenesis	HHV-8 preferentially infects B lymphocytes and endothelial cells and establishes latent infection in B cells. HHV-8 encodes a number of viral homologues of cell growth regulatory genes that promote angiogenesis, stimulate cell proliferation, and inhibit apoptosis. Uncontrolled expression of HHV-8 latency genes leads to cell transformation of endothelial cells and B-cell proliferation, culminating in vascular tumors and B-cell lymphomas.
Laboratory Diagnosis	HHV-8 infection is detected by PCR, in situ immunohistochemistry, or DNA hybridization.
Treatment and Prevention	There is no specific antiviral therapy for HHV-8 and no vaccine is available to prevent HHV-8 infection. Treatment of patients with underlying HIV/AIDS with highly active antiretroviral therapy (HAART) is key since HIV virologic reduction and immune system improvement may help improve KS disease. Systemic chemotherapy may be indicated for KS-associated malignancy, especially in cases of more advanced disease or rapid progression.
Notes	KS is the most common AIDS-associated malignancy.

A 9-year-old boy is seen in a pediatric practice with a chief complaint of multiple lumps on his face that have persisted for 2 weeks. Physical examination reveals multiple painless, flesh-colored, umbilicated nodules on the face and trunk without signs of inflammation.

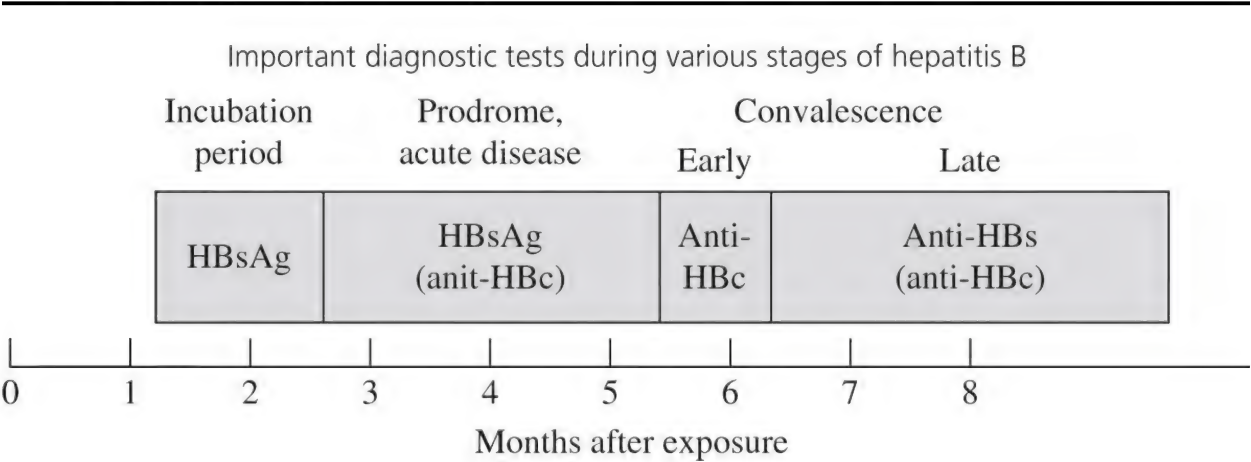


Multiple umbilicated, flesh-colored papules characteristic of this viral infection. (Reproduced, with permission, from Kasper D, Fauci A, Hauser S, Longo D, Jameson J, Loscalzo J. eds. *Harrison’s Principles of Internal Medicine* . 19th ed. New York: McGraw-Hill; 2015.)

Molluscum Contagiosum

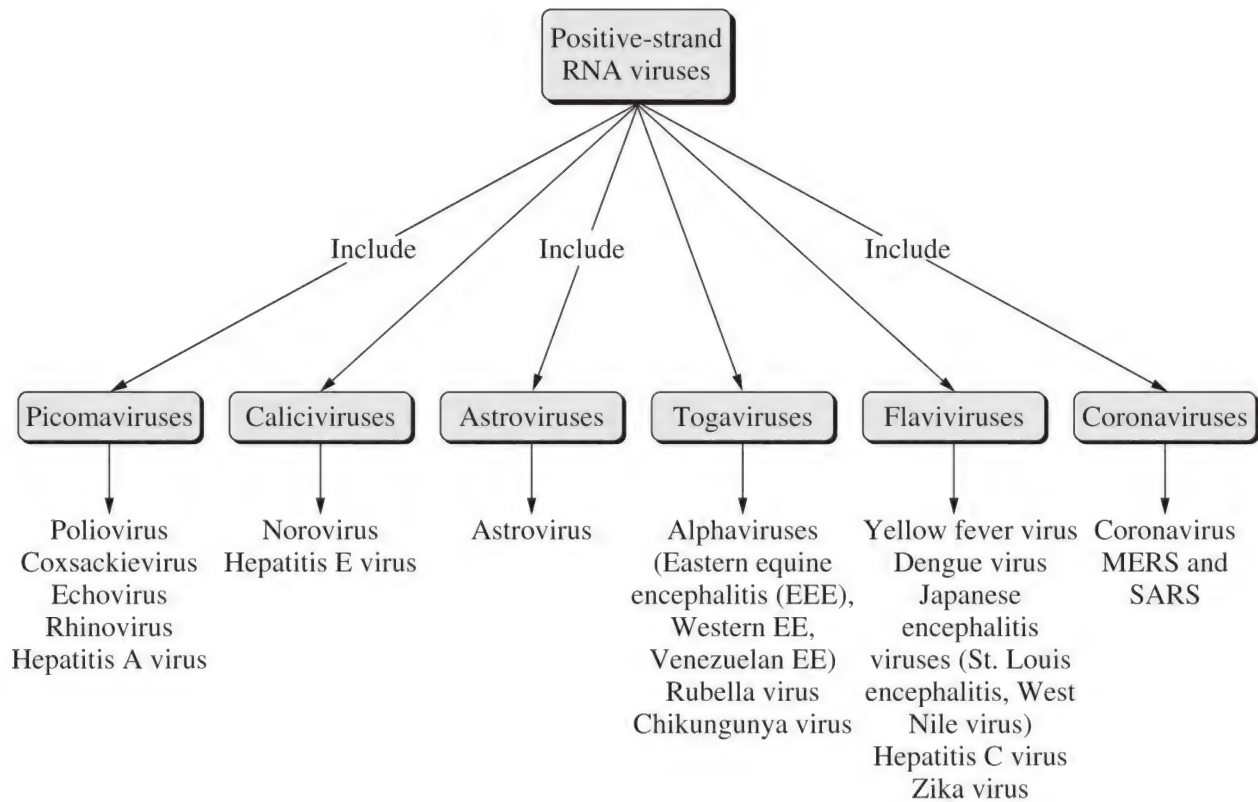
Etiology and Epidemiology	Molluscum contagiosum is caused by the poxvirus molluscum contagiosum virus (MCV) . MCV is transmitted by direct bodily contact . Genital MCV lesions can be transmitted sexually .
Clinical Manifestations	Molluscum contagiosum presents as benign nodular skin lesions that appear as pearly, flesh-colored, raised, umbilicated nodules without systemic symptoms. MCV lesions are painless and resolve over time.
Pathogenesis	MCV infects epidermal cells to form a localized, fleshy lesion with an umbilicated center. Because of its superficial location, MCV provokes a minimal inflammatory or immune response.
Laboratory Diagnosis	Diagnosis of MCV can be made by the histologic detection of eosinophilic cytoplasmic inclusions (molluscum bodies) in biopsy specimens of skin lesions.
Treatment and Prevention	There is no specific antiviral therapy for MCV. Curettage, cryotherapy, or topical agents are treatment options. There is no vaccine to prevent MCV infection.
Notes	

A 29-year-old man with a history of injection drug use is seen by an internist with complaints of fever, fatigue, nausea, loss of appetite, joint pain, and abdominal discomfort for the past few weeks. He reports that his urine is dark and his skin looks yellowish. On examination, he is jaundiced, with an enlarged and tender liver. Subsequent laboratory tests are positive for elevated liver enzymes and serum bilirubin. Serologic testing is positive for HBsAg and IgM anti-HBc.



Hepatitis B

Etiology and Epidemiology	Hepatitis B (HB) is caused by hepatitis B virus (HBV) . HBV is transmitted sexually , by blood and other bodily fluids , by injection drug use , and perinatally .
Clinical Manifestations	Clinical outcome and symptoms of HBV infection range from mild and self-limited to severe and chronic. Most primary infections are subclinical. Acute hepatitis , characterized by fever, fatigue, anorexia, nausea, and pain-associated hepatomegaly, occurs in 25%–35% of infected individuals. Symptoms indicative of more liver involvement include elevated liver enzymes, jaundice, pale stools, and dark urine. Markers of HBV infection—HB surface antigen (HBsAg), HBe antigen, and HBV DNA—are detected in serum. Chronic hepatitis occurs in about 10% of HBV infections and is defined as the detection of HBsAg, HBV DNA, and HBeAg for 6 months or more. Patients with chronic HB are at risk for liver cirrhosis, liver failure, and hepatocellular carcinoma .
Pathogenesis	HBV infects hepatocytes but does not cause direct cytopathology. Hepatocellular injury is due to immune attack by cytotoxic T cells. Individuals who fail to clear the virus from the body become virus carriers, and chronic hepatitis and cirrhosis result. Antibody to HBsAg is protective and cell-mediated immunity important in clearing infection.
Laboratory Diagnosis	HBV infection may be suspected initially by clinical presentation in combination with abnormal biochemical tests (liver enzymes, bilirubin), which prompt serologic assays. IgM antibody to HB core antigen (HBcAg) is an indicator of acute infection. The presence of antibody to HBsAg is associated with immunity to HBV infection. HBV genome and a quantitative viral load are determined by PCR assay.
Treatment and Prevention	There is no specific treatment for acute HB. Chronic HB is treated with pegylated interferon-alpha, tenofovir, or entecavir. Choice of antiviral agent may depend on whether the patient also has HIV infection and requires HAART. Timing and duration of treatment depends on viral load, liver enzyme abnormalities, and disease severity (eg, cirrhosis, liver failure). Active immunization against HBV is achieved with a recombinant HBsAg vaccine . Passive immunization with HBV immune globulin is given to neonates born to HBsAg (+) mothers and after needlestick exposures. Avoidance of high-risk behavior is an important preventive measure.



KEY CONCEPTS

- Positive-strand RNA viruses have single-stranded RNA genomes of the same polarity or sense as mRNA.
- The (+) strand RNA virus genome functions as mRNA, and the naked RNA is infectious.
- All (+) RNA viruses encode an RNA-dependent RNA polymerase used in genome replication. Unlike other RNA viruses, (+) RNA viruses do not carry

the polymerase as part of the virion structure.

- Medically important (+) RNA viruses encompass six virus families (Picornaviridae, Caliciviridae, Astroviridae, Togaviridae, Flaviviridae, and Coronaviridae) and share similar properties.

PROPERTIES OF POSITIVE-STRAND RNA VIRUSES

Virus Family	RNA Structure	Virion Polymerase	Shape	Envelope	Site of Replication	Human Viruses
Picornaviridae	Linear, ss (+) nonsegmented	No	Icosahedral	No	Cytoplasm	Poliovirus Coxsackievirus Echovirus Rhinovirus Hepatitis A virus
Caliciviridae	Linear, ss (-) nonsegmented	No	Icosahedral	No	Cytoplasm	Norovirus Hepatitis E virus
Astroviridae	Linear ss (+) nonsegmented	No	Icosahedral	No	Cytoplasm	Astrovirus
Togaviridae	Linear, ss (-) nonsegmented	No	Icosahedral	Yes	Cytoplasm	Alphaviruses (EEE, WEE, VEE viruses), Chikungunya virus, Rubella virus
Flaviviridae	Linear, ss (-) nonsegmented	No	Icosahedral	Yes	Cytoplasm	Yellow fever virus Dengue virus Zika virus JE, MVE, SLE, WN viruses Hepatitis C virus
Coronaviridae	Linear, ss (+) nonsegmented	No	Helical	Yes	Cytoplasm	Coronavirus, SARS, MERS

EEE, Eastern equine encephalitis; WEE, Western equine encephalitis; VEE, Venezuelan encephalitis; JE, Japanese encephalitis; MVE, Murray Valley encephalitis; SLE, St. Louis encephalitis; WN, West Nile.

A 10-year-old boy in Nigeria is seen by a CDC physician with a chief complaint of increasing weakness in one leg. Ten days earlier, he had a minor illness consisting of nausea and vomiting that was followed by a sensation of numbness in his left leg.



(a)

(b)

(c)

Viral cytopathic effects (CPE) in cell culture.

A Monolayer of normal unstained monkey kidney cells in culture.

B/C. Monkey kidney cell culture illustrating advanced CPE (Reproduced, with permission, from Carroll KC et al. *Jawetz, Melnick & Adelberg's Medical Microbiology* . 27th ed. New York: McGraw-Hill; 2015.)

Poliomyelitis

Etiology and Epidemiology	Poliomyelitis is caused by poliovirus. Poliovirus is transmitted by the fecal-oral route. Humans are the only natural hosts. Polio has been largely eradicated from the western hemisphere by vaccination. Fewer than 2000 cases of polio still occur each year, principally in Africa and the Indian subcontinent.
Clinical Manifestations	Most (90%–95%) poliovirus infections are asymptomatic. Abortive poliomyelitis is the most common clinical form and is characterized by a flu-like illness, with fever, headache, sore throat, and nausea followed by spontaneous recovery without CNS sequelae. A minority (~1%) of poliovirus infections result in either nonparalytic or paralytic poliomyelitis. Nonparalytic poliomyelitis is characterized by symptoms of aseptic meningitis with fever, headache, and stiff neck followed by spontaneous recovery. Paralytic poliomyelitis is characterized by asymmetric flaccid paralysis , most often affecting the legs. A post-polio syndrome is observed in about 25% of persons who survive paralytic poliomyelitis. The syndrome appears many years after full or partial recovery from acute polio infection and is characterized by constitutional, neurological, and musculoskeletal symptoms such as generalized fatigue, muscle or joint pain, and progressive muscle weakness with or without atrophy.
Pathogenesis	Poliovirus initiates infection in the pharynx and gastrointestinal tract after ingestion, spreads to the draining lymph nodes, and then reaches the CNS by viremic spread. CNS invasion results in direct killing of motor neurons located in the anterior horn of the spinal cord, with subsequent paralysis. Clearance of poliovirus and recovery from infection are primarily due to IgA and IgG antibody responses.
Laboratory Diagnosis	Poliovirus can be detected in cell culture and identified with poliovirus-specific antibody. The gold standard method for diagnosis is reverse-transcriptase (RT) PCR amplification of polio virus RNA from cerebrospinal fluid. RT-PCR is also used to discriminate between poliovirus and other enteroviruses.
Treatment and Prevention	There is no treatment for poliomyelitis. Polio can be prevented by either a live, attenuated (Sabin) or killed (Salk) vaccine. Killed polio vaccine is recommended in the United States because of rare cases of live vaccine-associated paralytic polio.
Notes	

A 14-year-old girl is seen in a pediatric practice with a sudden onset of fever (39.4°C), headache, stiff neck, and photophobia. She returned home last week from summer vacation at a recreational vehicle campsite that featured a campground pool.

Aseptic Meningitis

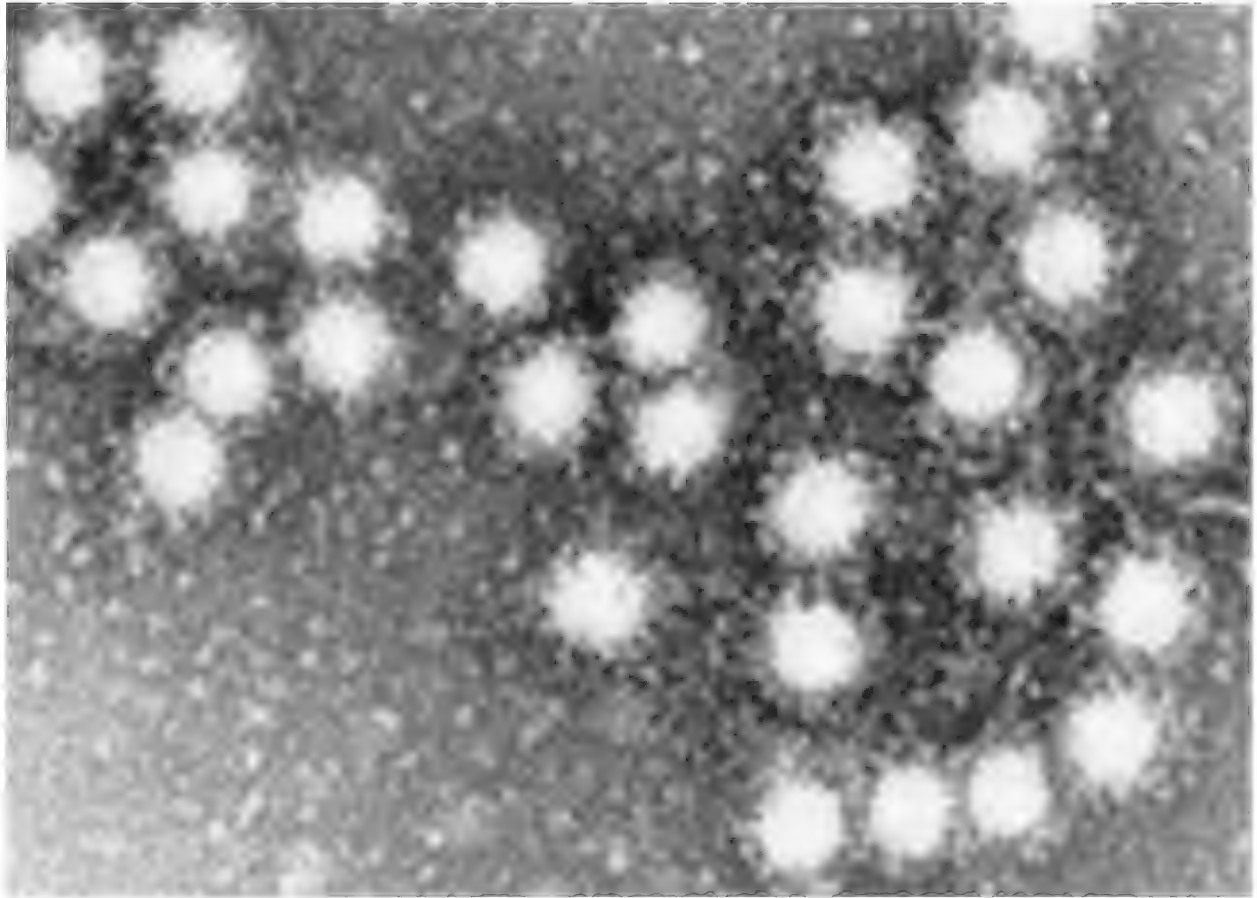
Etiology and Epidemiology	Nonpolio enteroviruses (coxsackieviruses and echoviruses) are a common cause of aseptic meningitis. Coxsackie and echoviruses are transmitted by the fecal-oral route and direct contact with infected secretions; less commonly by respiratory droplets. Coxsackie and echovirus infections are most common in the summer and fall months in temperate climates. Each virus has numerous serotypes.
Clinical Manifestations	Aseptic meningitis is characterized by acute onset of fever, headache, stiff neck, and photophobia. Most patients recover in about a week with no CNS sequelae. Other disease syndromes associated with coxsackieviruses and echoviruses include herpangina (coxsackie A and echovirus), hand-foot-and-mouth disease (coxsackie A), pleurodynia and myalgia (coxsackie B), acute hemorrhagic conjunctivitis (coxsackie A), and pericarditis and myocarditis (coxsackie B). Additionally, enterovirus D68 (EV-D68), while known for many decades, has recently been associated with clusters of cases of upper and lower respiratory infections in young children with CNS manifestations of acute motor neuron disease similar to poliomyelitis.
Pathogenesis	Coxsackievirus and echovirus pathogenesis is similar to that of poliovirus but differs by commonly infecting the meninges rather than the motor neurons. Virus directly damages and kills target cells. Clearance of the virus is antibody-mediated.
Laboratory Diagnosis	Coxsackieviruses, echoviruses, and other enteroviruses are detected and differentiated by PCR.
Treatment and Prevention	There is no treatment or vaccine for coxsackie, echovirus, or other enterovirus infection. Control measures include frequent handwashing and avoidance of sharing of towels and bedding with persons with conjunctivitis.
Notes	

An 18-year-old college student is seen in the university health clinic with complaints of sneezing, nasal discharge, nasal congestion, headache, sore throat, and cough for 3 days. Physical examination revealed an afebrile, normal-appearing male patient.

Common Cold

Etiology and Epidemiology	Rhinoviruses are the most frequent cause of the common cold. Rhinoviruses are transmitted by hand-to-nose or hand-to-eye contact with contaminated respiratory secretions or respiratory droplets . Rhinoviruses are distributed worldwide; more than 100 rhinovirus serotypes are known.
Clinical Manifestations	The common cold is characterized by an incubation period of 2–3 days followed by rhinorrhea, nasal congestion, sneezing, headache, mild pharyngitis, and cough, with little or no fever. Symptoms resolve after a week generally without complications.
Pathogenesis	Rhinoviruses gain entry to cells in the nasopharynx by attachment to the intercellular cell adhesion molecule-1 (ICAM-1) receptor. Replication is localized to nasal epithelial cells and virus is shed in respiratory secretions. The virus causes minimal pathology to respiratory epithelial cells. The major pathogenesis of rhinovirus infections is associated with chemical mediators of inflammation (bradykinin, prostaglandins) that cause vasodilation, mucus secretion, and stimulation of the sneeze and cough reflexes.
Laboratory Diagnosis	The common cold is a clinical diagnosis. It is often self-diagnosed by the patient who may or may not seek medical evaluation, depending on the severity of illness.
Treatment and Prevention	There is no treatment and no vaccine to prevent rhinovirus colds. Handwashing is an effective method of prevention.
Notes	

A 25-year-old man is seen in an outpatient clinic with a chief complaint of fatigue, nausea, and vomiting for the past several days. He has had noticed that morning that his urine was dark yellow. On physical examination, the patient is found to have a low-grade fever, jaundice, and mild abdominal pain. He denies intravenous drug use and having unprotected sex or multiple sexual partners. He attended a 5-day outdoor rock concert in North Carolina 3 weeks earlier. He is a cook at the local university dining hall.



Electron micrograph of 27 nm viral particles purified from stool of above patient. (Reproduced, with permission, from Kasper et al, eds. *Harrison's Principles of Internal Medicine* . 19th ed. New York: McGraw-Hill; 2015.)

Hepatitis A

Etiology and Epidemiology	Hepatitis A is caused by the picornavirus, hepatitis A virus (HAV) . HAV is transmitted by the fecal-oral route. Epidemics of HAV are usually due to food- or water-borne infections associated with poor sanitary conditions and personal hygiene.
Clinical Manifestations	Hepatitis A is characterized by an incubation period ranging from 15 to 50 days followed by the onset of fever, anorexia, nausea, vomiting, jaundice, and dark urine due to bilirubinuria. The duration of illness varies but is usually self-limiting with recovery in 3–4 weeks. Fulminant hepatitis leading to total liver failure and death is a rare complication.
Pathogenesis	Ingested HAV initially infects cells in the oropharynx and gastrointestinal tract, spreads to the liver by viremia, and infects hepatocytes without producing marked cytopathology. Hepatic cell injury is mediated by immune attack by cytotoxic T cells. Virus from infected liver cells is shed into the intestine and excreted in the feces. HAV does not establish a chronic infection or carrier state. Serum IgG is important in recovery from infection and in long-term protection.
Laboratory Diagnosis	HAV is detected by HAV-specific IgM antibody, which peaks during the acute or early convalescent stage of illness and remains detectable for approximately 3–6 months.
Treatment and Prevention	There is no treatment for HAV infection. An inactivated HAV vaccine is available for individuals at risk for HAV infection. Passive immunization with HAV immune globulin is recommended for post-exposure prophylaxis in individuals exposed to infection but not previously immunized. Handwashing is an effective means of prevention.
Notes	

A 12-year-old girl is seen by her pediatrician with symptoms of vomiting, diarrhea, nausea, stomach cramps, chills, and fever. Symptoms began 1 day after attending a school dinner and pool party at a local country club.

VIRAL CAUSES OF GASTROENTERITIS AMONG HUMANS

Virus	Family	Genome	Primary Age Group at Risk	Clinical Severity	Detection Assays
Group A rotavirus	Reoviridae	Double-strand segmented RNA	Children <5 years	+ + +	EM, EIA (commercial), PAGE, RT-PCR
Norovirus	Caliciviridae	Positive-sense single-strand RNA	All ages	+ +	EM, RT-PCR
Sapovirus	Caliciviridae	Positive-sense single-strand RNA	Children <5 years	+	EM, RT-PCR
Astrovirus	Astroviridae	Positive-sense single-strand RNA	Children <5 years	+	EM, EIA, RT-PCR
Adenovirus (mainly types 40 and 41)	Adenoviridae	Double-strand DNA	Children <5 years	+/+ +	EM, EIA (commercial), PCR

EIA, enzyme immunoassay; EM, electron microscopy; PAGE, polyacrylamide gel electrophoresis; PCR, polymerase chain reaction; RT-PCR, reverse-transcription PCR.

Acute Gastroenteritis

Etiology and Epidemiology	Noroviruses belong to the calicivirus family and are the most common cause of acute gastroenteritis in older children and adults in the United States. Noroviruses are transmitted by the fecal-oral route. Norovirus outbreaks are associated with the ingestion of contaminated food or water, direct person-to-person contact, and contact with contaminated environmental surfaces.
Clinical Manifestations	Acute gastroenteritis is characterized by acute onset of vomiting, diarrhea, nausea, abdominal cramps, and fever. Norovirus incubation period is short, usually 24–48 hours (range, 12–72 hours), and the onset of symptoms is typically very abrupt. The duration of illness is usually 48–72 hours with rapid recovery. Vomiting is a prominent symptom. Diarrhea is generally watery without blood or mucus.
Pathogenesis	Norovirus infects the small bowel and directly damages enterocytes. Norovirus-induced pathology leads to transient malabsorption of water and nutrients and reduced gastric motility, culminating in vomiting and diarrhea.
Laboratory Diagnosis	Norovirus is detected in clinical or environmental samples by reverse transcriptase-PCR.
Treatment and Prevention	There is no specific treatment or vaccine for norovirus infection. Supportive care is the mainstay of treatment. Handwashing and use of surface disinfectants are effective means of prevention.
Notes	

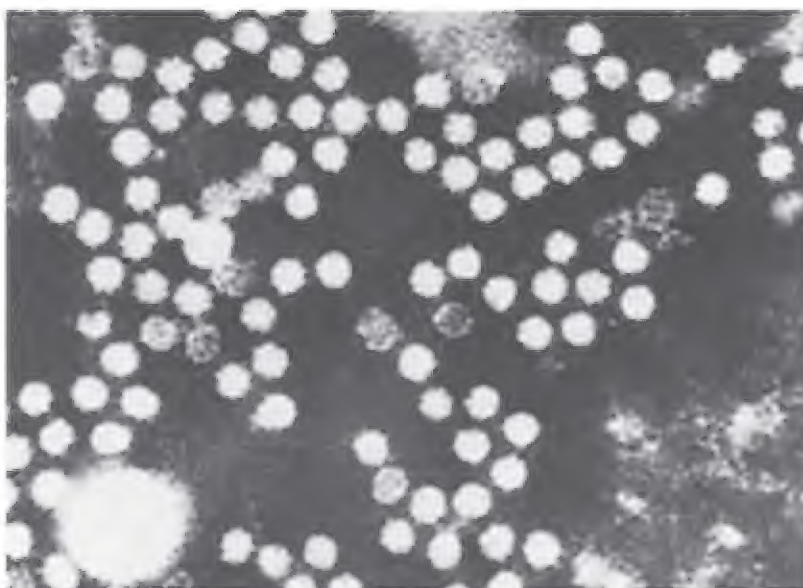
A 45-year-old male is seen in the Internal Medicine clinic with complaints of fatigue, anorexia, nausea, vomiting, and low-grade fever for the past 5 days. This morning, he noticed his urine was dark and stools were clay-colored. On examination, his liver was enlarged and tender. He recently returned from a week-long trip to Nepal.

Hepatitis E

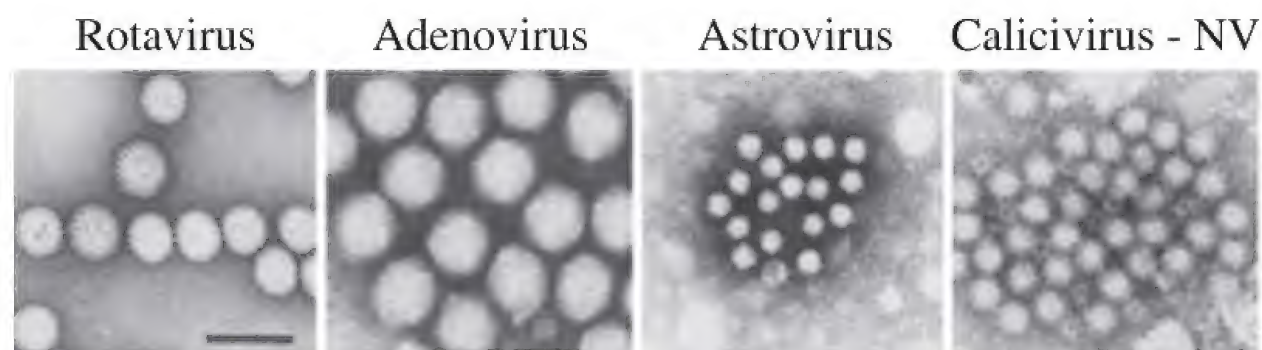
Etiology and Epidemiology	Hepatitis E is caused by the calicivirus, hepatitis E virus (HEV) . HEV is transmitted by the fecal-oral route and often spreads by sewage-contaminated drinking water. HEV is endemic and the most common cause of acute hepatitis in developing countries is poor sanitation. Recent travel to areas with endemic HEV infection is associated with clinical hepatitis E in developed countries.
Clinical Manifestations	Hepatitis E is clinically indistinguishable from the other forms of acute viral hepatitis with symptoms of malaise, fatigue, anorexia, nausea, vomiting, right upper quadrant abdominal pain, jaundice, and dark urine. Fulminant hepatitis is an especially lethal complication of HEV infections among pregnant females in the third trimester.
Pathogenesis	HEV pathogenesis is similar to that of HAV. HEV does not establish a chronic infection or carrier state.
Laboratory Diagnosis	Diagnosis of HEV is made by the detection of HEV-specific IgM or IgG antibody.
Treatment and Prevention	There is no specific treatment or vaccine for HEV. Improved sanitary conditions (e.g., boiling drinking water) would lower the rate of transmission.
Notes	

A 4-year-old child is seen in a pediatric practice with fever, vomiting,

abdominal pain, and watery diarrhea for 2 days. Laboratory findings were negative for rotavirus antigen.



Electron micrograph of viral particles purified from patient stool specimen.

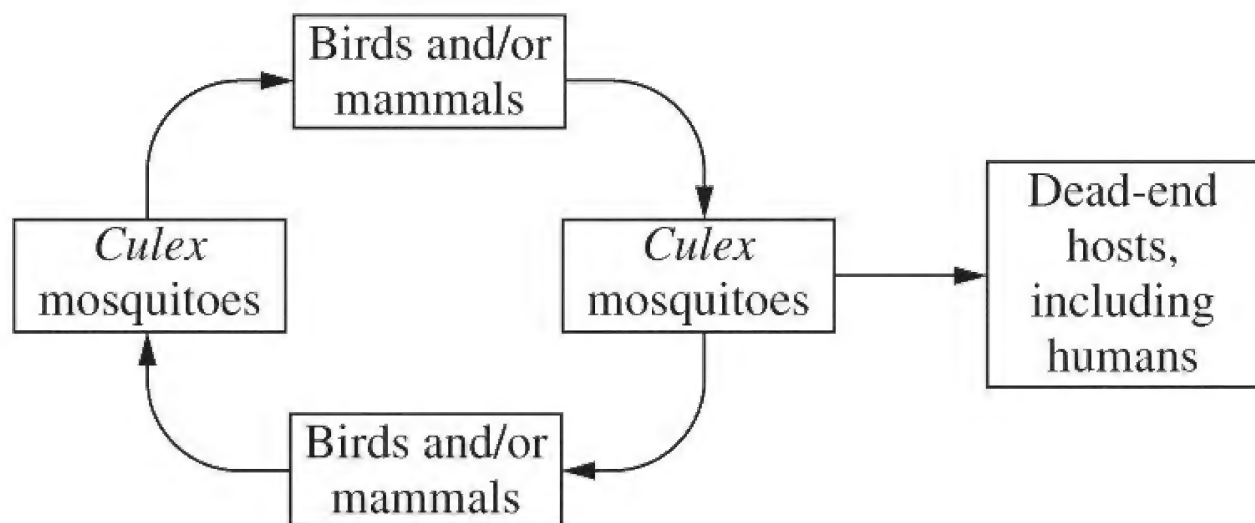


Viral agents of gastroenteritis. (NV, norovirus). (Reproduced, with permission, from Kasper et al, eds. *Harrison's Principles of Internal Medicine* . 19th ed. New York: McGraw-Hill; 2015.)

Acute Gastroenteritis

Etiology and Epidemiology	Astrovirus causes acute gastroenteritis primarily in infants and young children. Astroviruses are transmitted by the fecal-oral route. Astrovirus is second only to rotavirus as the cause of diarrhea in children.
Clinical Manifestations	Astrovirus acute gastroenteritis is characterized by vomiting, abdominal pain, fever, and watery diarrhea that is self-limiting. Astrovirus infection is generally less severe than rotavirus infection.
Pathogenesis	Astrovirus infects intestinal epithelial cells and directly damages enterocytes. Viral clearance and protective immunity are correlated with serum IgG antibody.
Laboratory Diagnosis	Astroviruses are detected by viral antigen assays and PCR.
Treatment and Prevention	Supportive care is the mainstay of treatment since there is no treatment or vaccine for astrovirus infection. Handwashing is an effective method of prevention.
Notes	

A 55-year-old man living on the eastern shore of Virginia is brought to the local health department clinic in August with a high fever, stiff neck, severe headache, and lethargy. There have been three cases of fatal EEE in horses reported in the county.



Transmission cycle of EEE virus.

Eastern Equine Encephalitis

Etiology and Epidemiology	Eastern equine encephalitis (EEE) is caused by eastern equine encephalitis virus , a member of the alphavirus genus in the togavirus family. Closely related alphaviruses are western equine encephalitis (WEE) and Venezuelan equine encephalitis (VEE) virus. Alphaviruses are arboviruses transmitted by the bite of infected <i>Aedes</i> and <i>Culex</i> mosquitoes . Alphaviruses are maintained and amplified in nature in wild birds (EEE and WEE) or small mammals (VEE). EEE is concentrated in the eastern half and WEE in the western part of the United States. VEE occurs in Central and South America.
Clinical Manifestations	EEE and WEE viruses cause encephalitis characterized by fever, headache, and myalgias that may progress to dizziness, vomiting, confusion, convulsions, coma, and death. VEE viruses cause encephalitis and pneumonitis that may be complicated by secondary bacterial infections. EEE is more severe clinically than WEE. Mortality from EEE is 35% with neurologic deficits in 35% of EEE survivors. Mortality from WEE is 4% and 1% from VEE with milder neurologic deficits.
Pathogenesis	Infection is initiated by the bite of an infected mosquito. Virus is spread by viremia and invades the CNS via capillary endothelial cells or the choroid plexus. Serum IgG confers protective immunity to alphavirus infections.
Laboratory Diagnosis	EEE, WEE, and VEE infections are diagnosed serologically by a rise in virus-specific antibody titer.
Treatment and Prevention	There is no specific treatment or vaccines for human EEE, WEE, or VEE infections. A killed vaccine is available to protect horses. Mosquito vector control, protective clothing, and insect repellent containing DEET are key preventive measures.
Notes	

A 40-year-old female returns from a 2-week trip to India where she traveled to various urban regions of the country for sightseeing. Approximately 3 days after returning she develops headache, malaise, and fevers (39.0–39.8°C). Approximately 2 days later, she also develops a rash on her face, trunk, and extremities, and experiences polyarthralgias involving multiple joints, especially of the hands, wrists, ankles, and knees. She presents to her primary care physician, and upon examination, she is found to have a fever of 39.2°C, tenderness and swelling of multiple joints, and a diffuse maculopapular rash located on her face, trunk, and extremities. Blood smears are negative for malaria. HIV testing is negative. Blood cultures are sent and are pending. Clinical laboratory findings reveal lymphopenia, thrombocytopenia, and transaminitis.

Chikungunya

Etiology and Epidemiology	Chikungunya virus is an alphavirus and a member of the Togaviridae family. The name “chikungunya” is derived from the Makonde language in Africa meaning “that which bends up” in reference to the stooped posture of the patient suffering from incapacitating arthralgias from the infection. Chikungunya virus is transmitted by the bite of infected mosquitoes , and less commonly, by maternal-fetal transmission, blood product transfusion, or organ transplantation. It is endemic in certain parts of West Africa, and outbreaks have occurred in Africa, Asia, Europe, islands in the Indian and Pacific Oceans, the Caribbean islands, and the Americas. A large outbreak occurred on Réunion island in 2005–2006 that affected over 260,000 people, over a third of the island’s population.
Clinical Manifestations	Chikungunya virus infection usually causes a self-limited illness that lasts about 7–10 days. The incubation period is typically 3–7 days, with a range of 1–14 days. Clinical manifestations typically include fever for 3–5 days, malaise, polyarthralgias, and rash. Polyarthralgias are a predominant feature and typically involve smaller joints of the fingers, hands, wrists, and ankles as well as larger joints, such as shoulders and knees. Occurrence of a patchy or diffuse macular or maculopapular rash on the face, trunk, and extremities is common. Severe complications can include respiratory failure, cardiovascular decompensation, hemorrhage, renal failure, and neurological manifestations such as meningoencephalitis or Guillain-Barré syndrome. In rare cases, relapse or persistence of symptoms may occur months after the initial infection. Laboratory abnormalities can include lymphopenia, thrombocytopenia, transaminitis, and elevated creatinine.
Pathogenesis	Chikungunya virus enters host cells by receptor-mediated endocytosis in clathrin-coated vesicles. The low pH of the endosome causes fusion of viral and host membranes, thus releasing the viral nucleocapsid into the host cell cytoplasm. Translation of the viral genome results in formation of a replication complex, which replicates and produces full length minus strand genome. Nonstructural viral proteins act as the plus strand replicase to produce plus strand RNA that encodes the protein precursors of the viral structural proteins. The structural proteins are processed in the Golgi complex and are then transported to the plasma membrane. The viral RNA is packed into nucleocapsids, and the mature virions bud out of the plasma membrane.
Laboratory Diagnosis	Chikungunya virus is detected by reverse transcriptase PCR assay or by serology.
Treatment and Prevention	Supportive therapy is the mainstay of care since there is no treatment for Chikungunya virus infection. Mosquito vector control, protective clothing, and insect repellent containing DEET are key preventive measures.
Notes	

A pregnant 16-year-old female living in Haiti was brought to the hospital in labor where she subsequently gave birth to a baby girl. The mother had a flu-like illness with a low-grade fever, maculopapular rash, and lymphadenopathy during the second month of pregnancy. On examination, the baby had a blueberry muffin-like rash and cataracts.



Widespread maculopapular lesions of a reddish-blue color. This presentation referred to as blueberry muffin baby. (Reproduced, with permission, from Lichtman MA et al. *Lichtman's Atlas of Hematology*. New York: McGraw-Hill; 2016.)

Congenital Rubella

Etiology and Epidemiology	Rubella virus, a member of the togavirus family, is the cause of congenital rubella syndrome. Rubella virus is transmitted postnatally by respiratory droplets of infected individuals. Congenital infections occur by transplacental transmission from infected mother to the fetus. Rubella virus is recognized as one of the most potent infectious teratogenic agents. Risk of congenital rubella syndrome is greatest during the first trimester of pregnancy but can occur throughout pregnancy. Rubella outbreaks in the United States are rare but occur in unvaccinated or undervaccinated populations in the United States or in countries where rubella vaccination is not routine. Rubella remains endemic in developing countries.
Clinical Manifestations	Rubella virus causes a mild illness in children and adults characterized by an incubation period of 14–21 days followed by a generalized maculopapular rash, low-grade fever, and lymphadenopathy. Common complications of postnatal rubella are arthritis and arthralgia, most frequently in adults. Rubella virus infection of women in the first trimester of pregnancy causes congenital rubella syndrome in the child, which is characterized by cataracts, cardiac abnormalities, deafness, and mental retardation.
Pathogenesis	In postnatal infections, rubella virus enters via the respiratory tract, spreads to local lymph nodes, then spreads to the spleen and regional lymph nodes and disseminates by viremia to the skin, kidneys, joints, and respiratory tract. In congenital rubella, the virus infects the placenta and spreads to the fetus with multiple organ involvement and teratogenic effects. Antibody response limits viral spread, but cell-mediated immunity is required to resolve infection.
Laboratory Diagnosis	Rubella virus-specific IgM and IgG antibody detection is the most common diagnostic test for rubella virus infection.
Treatment and Prevention	There is no specific treatment for rubella virus infection. Live, attenuated rubella virus vaccine is highly effective in preventing rubella. The vaccine is usually given as a combined measles, mumps, rubella (MMR) vaccine.
Notes	

A 45-year-old male Peruvian forestry worker is brought to the local health facility with a fever of 39.5°C, vomiting, and bleeding from his mouth. His presenting symptoms were preceded 3 days earlier with a high fever, headache, myalgias, and backache. On physical examination, the patient is jaundiced, bleeding from his nose and gums, and appears toxic.



Aedes aegypti mosquito: vector in transmission.

Hemorrhagic Fever

Etiology and Epidemiology	A hemorrhagic fever syndrome is caused by yellow fever (YF) virus , a flavivirus. YF virus is transmitted by the bite of infected <i>Aedes mosquitoes</i> . YF is endemic in Africa and South America but is not present in the United States.
Clinical Manifestations	YF virus causes hemorrhagic fever that is characterized by fever, headache, jaundice, myalgias, black vomit or hematemesis, other hemorrhages, and shock. The mortality rate is 20%–50%.
Pathogenesis	YF virus is inoculated directly into the bloodstream by an infected mosquito and spreads to cells of the monocyte-macrophage lineage with liver as the target organ. Antibody and cell-mediated immunity are important in controlling infection.
Laboratory Diagnosis	YF virus infection is diagnosed by detection of virus-specific IgM antibody using an enzyme-linked immunosorbent assay (ELISA) or by detection of viral nucleic acid in blood or tissue by PCR assay.
Treatment and Prevention	Supportive care is the mainstay of treatment since there is no specific treatment for YF virus infection. A highly effective live, attenuated YF virus vaccine is available for prevention. Mosquito vector control, protective clothing, and insect repellent containing DEET are key preventive measures.
Notes	

A 24-year-old medical student is seen by her primary care physician because of sudden onset of fever (40°C), chills, severe headache, pain around the eyeballs, and muscle and bone pain. On examination, she has a faint, generalized macular rash. She returned to the United States 2 days earlier from a tropical medicine elective in the Caribbean Islands.



Aedes aegypti: mosquito vector in disease transmission. (Source: Centers for Disease Control and Prevention, Washington, DC.)

Dengue Fever (Breakbone Fever)

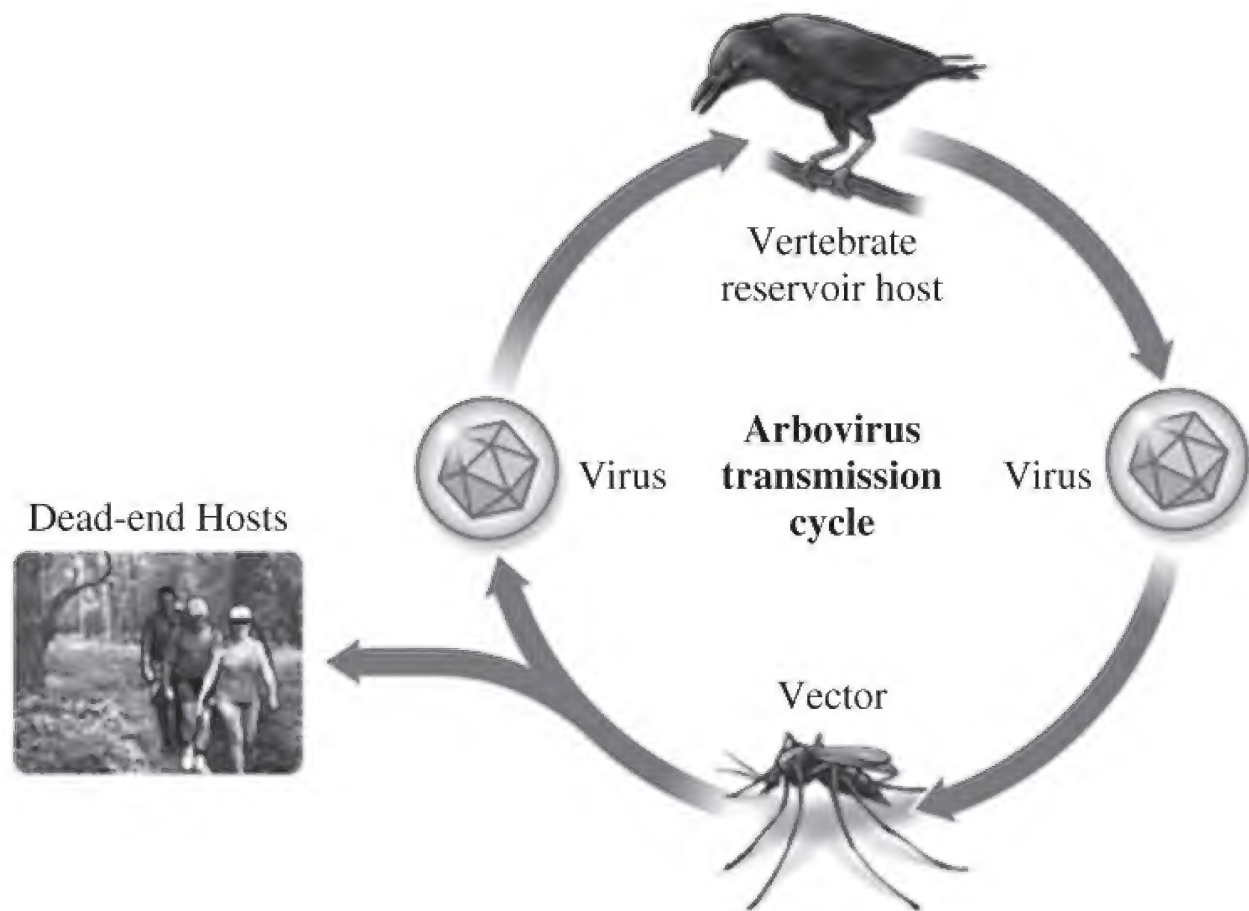
Etiology and Epidemiology	Dengue virus , a member of the flavivirus family, causes dengue fever . Four serotypes of the virus exist. Dengue is transmitted by the bite of infected <i>Aedes</i> mosquitoes . Dengue viruses are endemic in southeast Asia, Central and South America, and the Caribbean Islands. Locally acquired cases have occurred in the United States in Puerto Rico, Texas, and Florida where the mosquito vectors exist.
Clinical Manifestations	Dengue fever is an acute febrile disease with headache, retro-orbital or ocular pain, rash, myalgias, and deep bone pain ("breakbone fever"). Dengue fever may be mild or severe but rarely fatal. Dengue virus can also cause dengue hemorrhagic fever or dengue shock syndrome , characterized by symptoms of dengue fever that progress to fluid accumulation (ascites, pleural effusion), prostration, gastrointestinal, mucosal, and skin hemorrhages, shock, coma, and death in up to 10% of victims. The risk of hemorrhagic fever is higher during infection with a second dengue virus serotype. Depending on the severity of disease, abnormalities in laboratory testing may include leukopenia, thrombocytopenia, elevated hematocrit, and/or transaminitis.
Pathogenesis	Dengue virus is inoculated directly into the bloodstream by an infected mosquito and spreads to cells of the monocyte-macrophage lineage with the vasculature as the target organ. Serum antibody and cell-mediated immunity limit the outcome and severity of dengue fever and confer long-term protection. Dengue hemorrhagic fever-shock syndrome has an immunopathologic basis characterized by lymphocyte activation, release of cytokines, complement activation, and tissue damage.
Laboratory Diagnosis	A presumptive diagnosis of dengue virus infection is usually made clinically. Dengue virus infection is confirmed by virus-specific IgM antibody using enzyme-linked immunosorbent assay (ELISA) or by detection of viral nucleic acid by reverse-transcriptase PCR.
Treatment and Prevention	Supportive therapy is the mainstay of care since there is no specific treatment or vaccine for dengue virus. Mosquito vector control, protective clothing, and insect repellent containing DEET are key preventive measures.
Notes	

A 36-year-old male resident of St. Louis recently returned from Brazil where he attended Carnival. Approximately 1-week after returning, he experienced a low-grade fever, arthralgias involving the hands and feet, and a pruritic rash on his trunk and extremities. He went to his primary care physician. On physical examination, he was found to have a fever of 38.5°C, a nonpurulent conjunctivitis, tenderness of multiple joints, and a maculopapular rash located on his trunk, extremities, and on the palms of his hands and soles of his feet. Prior to becoming symptomatic, he was sexually active with his wife who just found out that she is pregnant and in her first trimester.

Zika virus

Etiology and Epidemiology	Zika virus is a member of the flavivirus family and causes disease similar to dengue virus. Zika virus is transmitted by the bite of infected <i>Aedes</i> mosquitoes, maternal-fetal transmission , sexual transmission , blood product transfusion , organ transplantation, or as a laboratory-acquired infection. Outbreaks of Zika virus have occurred in Africa, southeast Asia, and the Pacific Islands with the most recent outbreak occurring in Central and South America, the Caribbean Islands, and regions of the United States.
Clinical Manifestations	<p>Zika virus infection causes a mild, self-limited illness in the majority of cases. The incubation period is estimated to be 3–12 days. While the spectrum of Zika virus disease overlaps with other arboviral infections such as dengue virus infection, the rash of Zika virus infection predominates. Zika virus infection in adults and children often involves acute onset of symptoms including low-grade fever, nonpurulent conjunctivitis, arthralgias, and a pruritic maculopapular rash that typically involves the trunk, extremities, palms of the hands, and soles of the feet. The patient may also experience headache, retro-orbital discomfort or pain, myalgias, and generalized weakness, or less commonly, nausea, abdominal pain, diarrhea, and/or ulcerations of mucous membranes.</p> <p>Zika virus infection has been associated with a number of serious complications, including congenital microcephaly and fetal losses in women infected during pregnancy. Neurologic complications in adults and children can include Guillain-Barré syndrome.</p>
Pathogenesis	Viral attachment to unidentified host receptors is mediated by the Zika virus E (envelope) glycoprotein, followed by endocytic uptake, uncoating of the virus nucleocapsid, and release of viral RNA into the cytoplasm. Immature virions collect in the endoplasmic reticulum and in secretory vesicles before being released by the host cell.
Laboratory Diagnosis	Zika virus nucleic acid is detected by reverse transcription PCR assay.
Treatment and Prevention	Supportive therapy is the mainstay of care since there is no treatment for Zika virus infection. Mosquito vector control, protective clothing, and insect repellent containing DEET are key preventive measures.
Notes	

A 67-year-old man from Florida was admitted to the hospital in September with symptoms of high fever, headache, neck stiffness, and disorientation. The patient was well until 3 days ago when he developed a mild flu-like illness. He works part-time in the evenings for a landscaping firm. HSV by PCR and West Nile virus IgM assay of the CSF were negative.

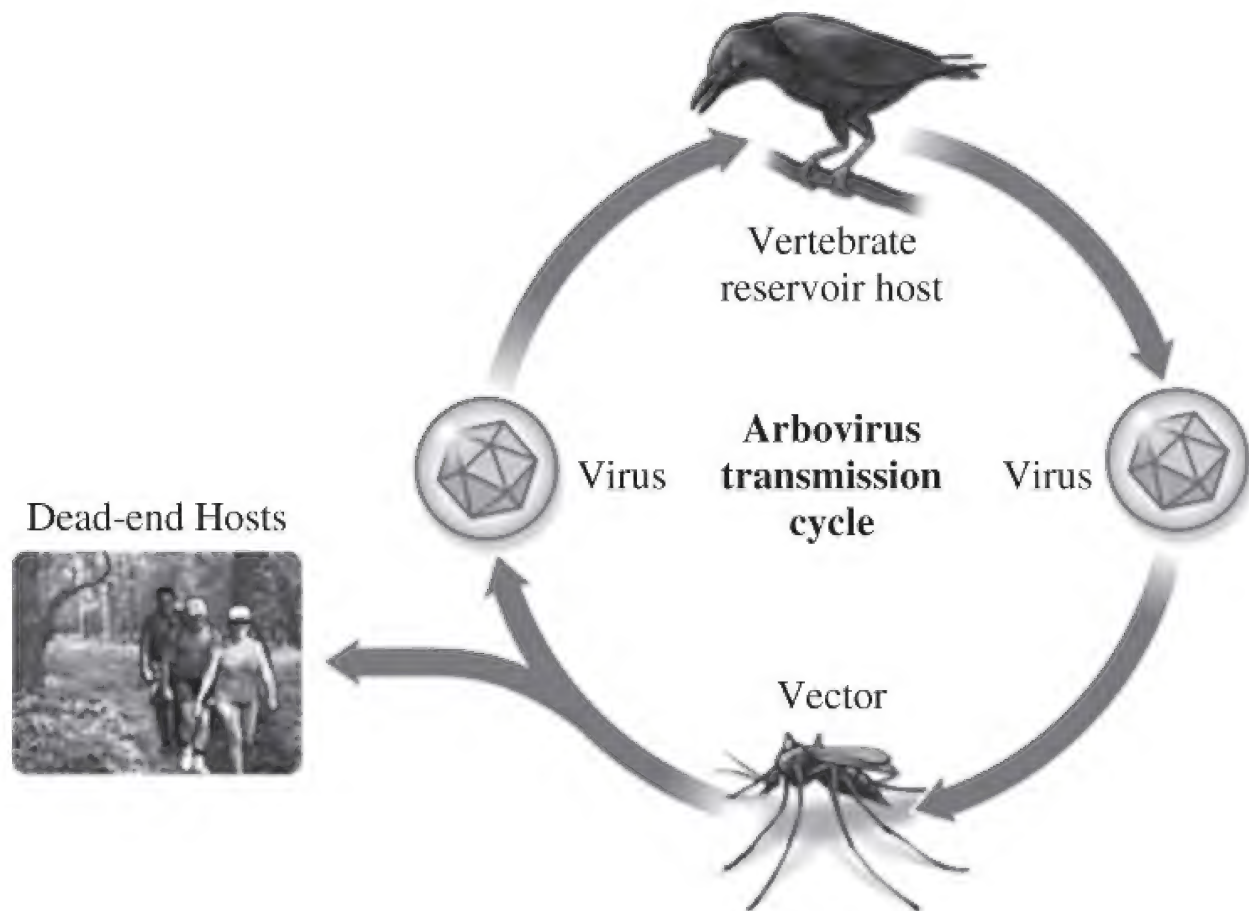


Arboviruses cycle between vertebrate reservoir host (bird) and vector (mosquito). Vector can also bite other hosts (humans), dead-end hosts. (Source: Centers for Disease Control and Prevention, Washington, DC.)

St. Louis Encephalitis

Etiology and Epidemiology	St. Louis encephalitis (SLE) is caused by the flavivirus, SLE virus . SLE virus is transmitted by the bite of infected <i>Culex</i> mosquitoes . SLE outbreaks occur throughout the United States primarily in late summer and early fall.
Clinical Manifestations	SLE virus causes clinical illness ranging from a nonspecific flu-like febrile illness to encephalitis . Symptoms in more severe infections include headache, nausea, high fever, malaise, myalgia, backache, neck stiffness, and disorientation. Mortality rate of SLE ranges from 3%–30%, with the elderly at increased risk.
Pathogenesis	The virus is inoculated directly into the bloodstream by an infected mosquito and then spreads to cells of the monocyte-macrophage lineage with the brain as the target organ. Virus spreads to the CNS via capillary endothelial cells or the choroid plexus. Antibody and cell-mediated immunity are important in controlling infection.
Laboratory Diagnosis	SLE virus is diagnosed by the detection of virus-specific IgM in serum or CSF.
Treatment and Prevention	There is no specific treatment or vaccine for SLE. Mosquito vector control, protective clothing, and insect repellent containing DEET are key preventive measures.
Notes	SLE is related antigenically to a group of flaviviruses that includes Japanese B encephalitis virus (Asia), Murray Valley encephalitis virus (Australia), and West Nile virus (Africa, Europe, Middle East, India, Australia, North America).

A 70-year-old man from western Pennsylvania was admitted to the hospital in August with complaints of fever, nausea, vomiting, headache, confusion, ataxia, and muscle weakness. According to the patient's daughter, he had been healthy until 2 days ago when he complained of flu-like symptoms including fever, neck stiffness, and vomiting. His history was significant for hypertension. He has no recent travel outside the area, is retired, and is an avid fisherman. An epidemic of dead crows has been reported in the county.



Arboviruses cycle between vertebrate reservoir host (bird) and vector (mosquito). Vector can also bite other hosts (humans), dead-end hosts. (Source: Centers for Disease Control and Prevention, Washington, DC.)

West Nile Encephalitis

Etiology and Epidemiology	West Nile encephalitis is caused by West Nile virus (WNV) , a flavivirus and is the most common cause of neuroinvasive arboviral disease in the United States. WNV is transmitted by the bite of infected <i>Culex</i> , <i>Aedes</i> , or <i>Anopheles</i> mosquitoes . Other documented routes of transmission include blood transfusion, organ transplantation, transplacental, and breast-feeding. Outbreaks of WNV infections in the United States occur usually in the late summer and early fall.
Clinical Manifestations	Asymptomatic infections with WNV are common. Clinical illness can range from nonspecific flu-like febrile illness to encephalitis . Symptoms in more severe infections include high fever, headache, nausea, malaise, myalgias, backache, neck stiffness, and disorientation. Mortality rate of WNV infection is about 10%, with young children and the elderly at increased risk.
Pathogenesis	WNV is inoculated directly into the bloodstream by an infected mosquito and then spreads to cells of the monocyte-macrophage lineage with the brain as the target organ. Virus spreads to the CNS via capillary endothelial cells or the choroid plexus. Pathogenesis is mediated by resistance to interferon. Antibody and cell-mediated immunity are important in controlling infection.
Laboratory Diagnosis	WNV is diagnosed by the detection of virus-specific IgM in serum or CSF.
Treatment and Prevention	There is no specific treatment or vaccine for WNV infection. Mosquito vector control, protective clothing, and insect repellent containing DEET are key preventive measures.
Notes	WNV virus is related antigenically to a group of flaviviruses that includes Japanese B encephalitis virus (Asia), Murray Valley encephalitis virus (Australia), and St. Louis encephalitis virus (North America, Central America, South America).

A 58-year-old white male is seen by his primary care physician with complaints of fever, abdominal pain, and dark urine. Past history is significant for injection drug use and alcohol abuse. On examination, he has a fever, jaundice, and hepatomegaly. Hepatitis B (HBV) serology is negative.

CLINICAL FEATURES OF HEPATITIS VIRUSES

Virus	Mode of Transmission	Chronic Carriers	Laboratory Test Usually Used for Diagnosis	Vaccine Available	Immune Globulins Useful
HAV	Fecal-oral	No	IgM HAV	Yes	Yes
HBV	Blood, sexual, at birth	Yes	HBsAg, HBsAb, IgM HBcAb	Yes	Yes
HCV	Blood, sexual ¹	Yes	HCV Ab	No	No
HDV	Blood, sexual ¹	Yes	Ab to delta Ag	No	No
HEV	Fecal-oral	No	None	No	No

Ab = antibody; Ag = antigen.

¹ Sexual transmission seems likely but is poorly documented.

Hepatitis C

Etiology and Epidemiology	Hepatitis C is caused by hepatitis C virus (HCV) , a flavivirus. HCV is transmitted parenterally by exposure to blood and blood products. Intravenous drug users and organ transplant recipients are at high risk for HCV infection. Sexual and maternal–fetal routes of transmission are less common for HCV. HCV is distributed worldwide, and HCV is the leading cause of liver cancer and liver transplants in the United States.
Clinical Manifestations	HCV causes acute and chronic hepatitis ; HCV infection predisposes individuals to the development of hepatocellular carcinoma . Primary HCV infections are asymptomatic or result in a mild illness with non-specific symptoms and rare jaundice. Chronic hepatitis develops in 75% of HCV infections and may progress to liver cirrhosis with an elevated risk for hepatocellular carcinoma.
Pathogenesis	HCV infects hepatocytes with liver injury mediated by cytotoxic T cells that contribute both to inflammation and viral clearance. Hepatocellular carcinoma linked to HCV infections is indirect (ie, the virus does not encode an oncogene) and is likely due to compensatory hepatocyte proliferation because of liver injury, thus providing a pool of dividing cells susceptible to genetic mutations. HCV can mutate at high frequency, creating variations in the major envelope protein and allowing escape from virus-neutralizing antibodies.
Laboratory Diagnosis	HCV is diagnosed most commonly by the detection of anti-HCV antibodies or reverse transcriptase PCR for detection of virion RNA and determination of viral load.
Treatment and Prevention	Treatment of chronic HCV with a combination of direct-acting agents (eg, sofosbuvir and ledipasvir) offers the prospect of a cure for the disease. There is no vaccine for HCV. Screening blood products and avoiding intravenous drug use are important in preventing HCV infection.

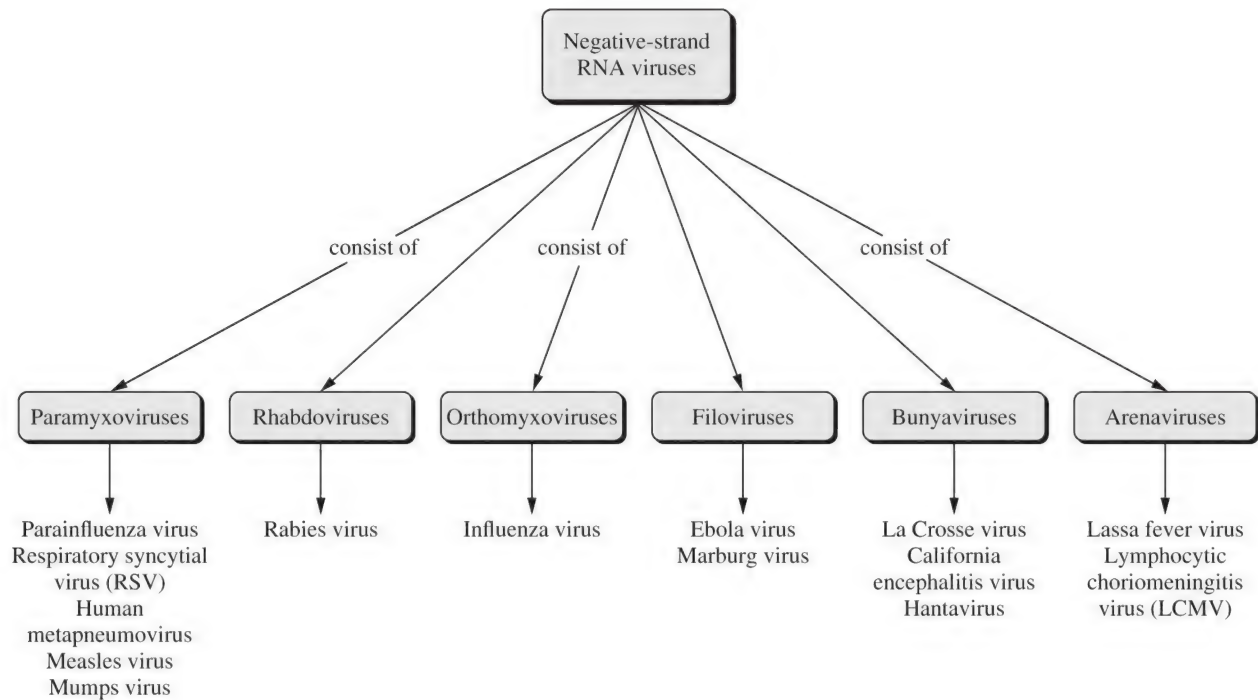
A 40-year-old male healthcare worker went to the emergency department in a local hospital with complaints of fever, cough, and shortness of breath and was admitted to the hospital. He lived and worked during the past year as a healthcare provider in Saudi Arabia. On physical examination, he has a fever of 38.3°C, dyspnea, and a dry cough. Bilateral lung infiltrates are seen on chest radiograph.



Electron micrograph of human coronavirus. Note prominent club-shaped spikes in the form of a corona (halo).

Middle East Respiratory Syndrome (MERS)

Etiology and Epidemiology	MERS is caused by a novel coronavirus (CoV) . Previously known coronaviruses cause about 30% of cases of the common cold and severe acute respiratory syndrome (SARS) . MERS-CoV affects all age groups and is transmitted by respiratory droplets produced by coughing or sneezing. Transmission requires close personal contact such as caring for, or living with, an infected individual. Infection may also be spread nosocomially or by infected camels, which are a natural host for MERS-CoV. MERS was first reported in 2012 in Saudi Arabia and has since spread to several other countries including the United States. As of January 2016, there had been approximately 1600 cases of confirmed MERS and nearly 600 deaths. No cases have been reported in the United States since 2014.
Clinical Manifestations	MERS is characterized by an incubation period of 5–7 days followed by the onset of high fever, chills or rigors, cough, and shortness of breath. Chest radiographs may reveal bilateral infiltrates.
Pathogenesis	MERS-CoV binds to the CD 26 receptor on respiratory epithelial cells and gains entry into the host cell. Lymphopenia and thrombocytopenia are common hematologic features of MERS.
Laboratory Diagnosis	MERS-CoV can be identified by reverse transcription PCR and by serologic tests to detect CoV-specific antibody.
Treatment and Prevention	There is no specific treatment or vaccine for MERS-CoV. Preventive measures to contain the spread of MERS-CoV are to isolate persons who are ill and to quarantine persons who have been exposed to MERS-CoV. Measures to prevent the spread and exposure of MERS-CoV include frequent handwashing, travel restrictions to areas with MERS, and the use of personal protective equipment by healthcare workers. Persons living within MERS-endemic areas should avoid close contact with camels.



KEY CONCEPTS

- Negative-strand (–) RNA viruses have single-stranded (ss) RNA genomes complementary to mRNA (ie, they are of negative polarity and are incapable of acting as mRNA).
- All (–) RNA viruses carry a virion-associated, RNA-dependent RNA polymerase that transcribes genomic RNA into mRNA. The same polymerase synthesizes a full-length, positive-strand copy of the viral RNA genome that acts as a template for new (–) RNA genomes.
- Medically important (–) RNA viruses are a diverse collection of six virus

families (Paramyxoviridae, Rhabdoviridae, Orthomyxoviridae, Filoviridae, Bunyaviridae, Arenaviridae) that share similar characteristics.

PROPERTIES OF NEGATIVE-STRAND RNA VIRUSES

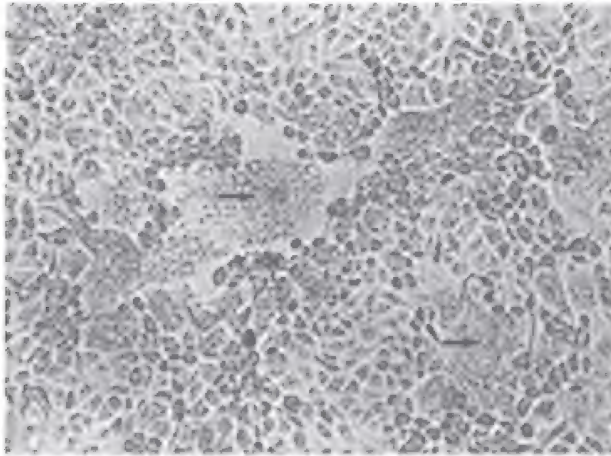
Virus Family	RNA Structure	Virion Polymerase	Shape	Envelope	Site of Replication	Human Viruses
Paramyxoviridae	Linear, ss (-) nonsegmented	Yes	Helical	Yes	Cytoplasm	Parainfluenza, RSV, Measles, Mumps
Rhabdoviridae	Linear, ss (-) nonsegmented	Yes	Helical Bullet-shaped	Yes	Cytoplasm	Rabies
Orthomyxoviridae	Linear, ss (-) segmented	Yes	Helical	Yes	Nucleus	Influenza
Filoviridae	Linear, ss (-) nonsegmented	Yes	Helical filamentous	Yes	Cytoplasm	Ebola, Marburg
Bunyaviridae	Circular, ss (-) segmented	Yes	Helical	Yes	Cytoplasm	LaCrosse, California encephalitis, Hantavirus
Arenaviridae	Circular, ss (-) segmented	Yes	Helical	Yes	Cytoplasm	Lassa fever, LCM

A 2-year-old child is brought to the Emergency Department by worried parents because of a barking cough and inspiratory stridor that got worse at night. The present illness began 2 days earlier with a fever, sore throat, rhinorrhea, and mild cough. Findings on examination include a temperature of 38.9°C, tachypnea, wheezing, and respiratory distress.

Croup

Etiology and Epidemiology	Parainfluenza viruses (PIV) type 1 and 2 are the major cause of croup (laryngotracheobronchitis) in infants and young children. PIV is transmitted by respiratory droplets or by direct contact with secretions or fomites. Reinfections are common, and immunity is transient.
Clinical Manifestations	There are four known PIV serotypes (PIV 1–4). Croup (PIV 1 and 2) is characterized by a fever, hoarseness, a barking cough, and inspiratory stridor. PIV 3 is associated with bronchiolitis and pneumonia in infants and young children. PIV 4 causes a mild upper respiratory illness in children and adults.
Pathogenesis	PIV infects and damages respiratory epithelial cells without systemic spread. Histopathologic changes include the presence of multinucleated giant cells caused by the viral fusion protein, a virulence factor that mediates direct cell-to-cell spread and promotes evasion from host antibody.
Laboratory Diagnosis	PIV diagnosis can be achieved by rapid, direct detection of viral antigen in cells of nasal aspirates or by isolation in cell culture and identification by PIV-specific antibodies.
Treatment and Prevention	There is no specific treatment or vaccine for PIV.
Notes	

A 6-week-old infant is brought to the pediatric clinic in respiratory distress. Physical examination is significant for diffuse expiratory wheezing and mild cyanosis. The chest X-ray is suggestive of bilateral pneumonia. The infant is admitted to the intensive care unit. A nasopharyngeal swab specimen is sent for respiratory viral panel testing, and nasopharyngeal washings are sent for culture and direct examination.



(a)



(b)

Virus-induced syncytial formation. Syncytia result from cell fusion with formation of multinucleated giant cells. (Reproduced, with permission, from Carroll KC et al. *Jawetz, Melnick & Adelberg's Medical Microbiology*. 27th ed. New York: McGraw-Hill; 2015.)

RSV Infection

Etiology and Epidemiology	Respiratory syncytial virus (RSV) is the most common cause of bronchiolitis and pneumonia in infants and children under age 1. RSV infections are transmitted by respiratory droplets and by direct contact with contagious secretions. Community outbreaks of RSV infection occur annually in late fall to early spring. Infants at high risk of mortality from RSV include neonates, premature infants, and infants with cardiopulmonary disease or those immunologically compromised. Reinfection with RSV is common in children and adults.
Clinical Manifestations	Bronchiolitis in infants is characterized by a pronounced cough, expiratory wheezing, and cyanosis. Otitis media is the most common complication of RSV infection in infants. RSV causes nonspecific upper respiratory tract disease in healthy adults. RSV causes an influenza-like syndrome in elderly patients.
Pathogenesis	RSV infection is localized primarily to the lower respiratory tract in infants without viremia or systemic spread. Multinucleated giant cells are a common histopathologic finding in pulmonary specimens. The narrow airway of infants is readily obstructed by virus-induced pathology. Severe disease in infants may have an immunologic basis (eg, tissue injury from inflammatory cytokines).
Laboratory Diagnosis	RSV diagnosis can be achieved by rapid, direct detection of RSV antigen in nasal aspirates or by isolation in cell culture and identification by RSV-specific antibody. RT-PCR assays are available for detection of RSV, often included as part of a respiratory viral panel (RVP) multiplex PCR assay that can detect multiple respiratory pathogens. RT-PCR assays provide an alternative to culture for confirming the result of rapid antigen detection assay.
Treatment and Prevention	For immunocompromised adults with severe RSV lower respiratory tract infection, ribavirin in combination with passive immunotherapy (monoclonal antibody (palivizumab) or hyperimmune globulin) and/or corticosteroids may be beneficial. For infants and young children (<2 years old), supportive care is the mainstay of treatment as ribavirin and/or corticosteroids are not recommended, and passive immunotherapy has not yet shown a proven benefit in this age group.

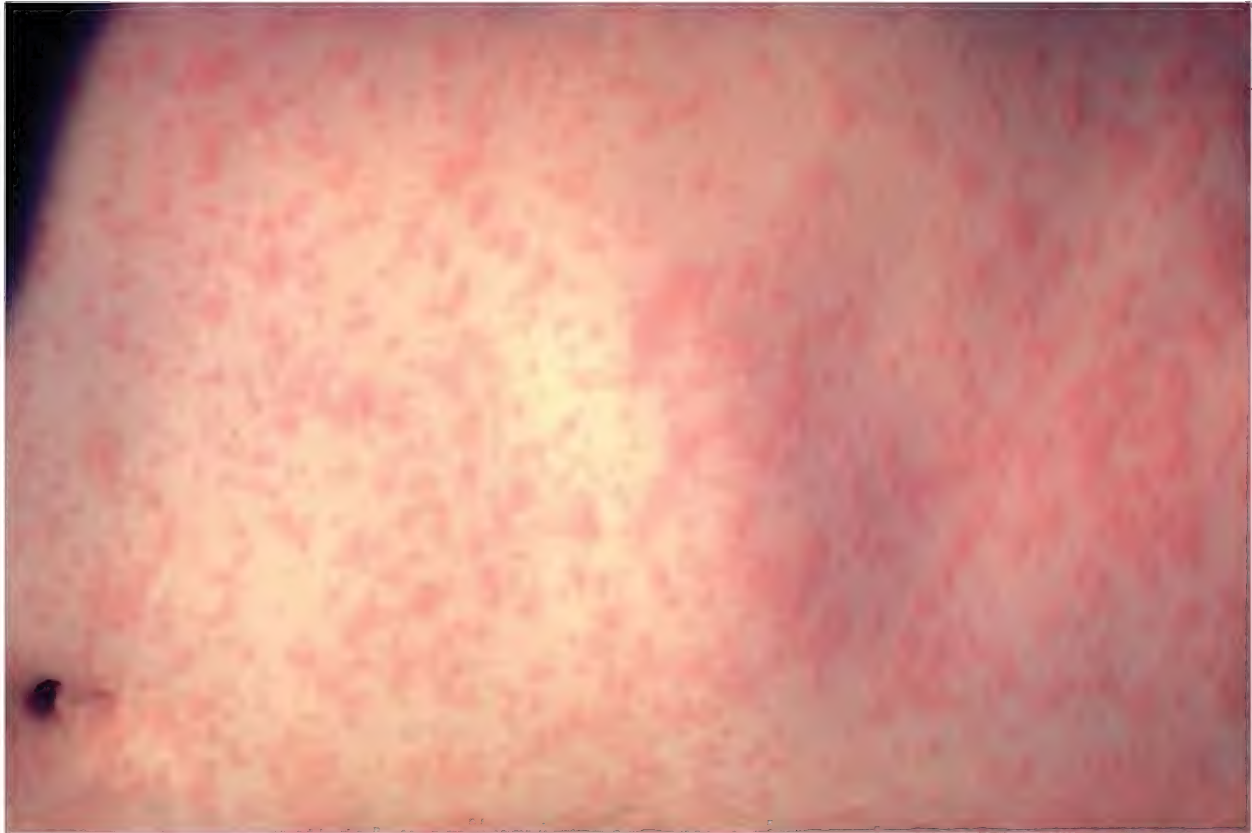
Notes

An 11-month-old baby boy is seen in a pediatric practice in February with symptoms of a nonproductive cough, nasal congestion, rhinorrhea, fever, and irritability. Physical examination was significant for a temperature of 38.6°C, rhinitis, and wheezing. A chest X-ray revealed pulmonary infiltrates. The child was admitted to the intensive care unit. Nasopharyngeal washings were negative for RSV.

Human Metapneumovirus Bronchiolitis

Etiology and Epidemiology	Human metapneumovirus (HMPV) , a paramyxovirus, is a cause of bronchiolitis and pneumonia in infants. HMPV was discovered in 2001 and has a worldwide distribution. The route of transmission is unknown but presumably is by respiratory droplets. The seasonality of HMPV infections is similar to RSV and influenza with recurrent epidemics during the winter months.
Clinical Manifestations	Clinical symptoms associated with HMPV infection in infants and children are similar to RSV disease characterized by cough, rhinorrhea, wheezing, fever, dyspnea, bronchiolitis, and pneumonia. HMPV infections tend to be slightly milder than RSV infections. Otitis media is associated with HMPV infections of children. Elderly adults and immunocompromised individuals are also at risk for mild or severe HMPV infection. HMPV may cause mild respiratory tract infections in the general community.
Pathogenesis	HMPV infects respiratory epithelial cells and targets the respiratory tract. The pathogenesis of HMPV infection is incompletely understood but likely parallels RSV infection.
Laboratory Diagnosis	HMPV infections are diagnosed by RT-PCR assay of respiratory clinical specimens.
Treatment and Prevention	There is no specific treatment or vaccine for HMPV infection.
Notes	

A 20-year-old college student is seen in the student health clinic with complaints of high fever, cough, and conjunctivitis. Physical examination reveals small vesicular lesions on an inflamed buccal mucosa and a rash on her face that is spreading to her trunk. She returned from a trip to India 2 weeks earlier. She is unvaccinated because of a personal belief exception.



Skin of patient with rash. (Source: Centers for Disease Control and Prevention, Washington, DC.)

Measles

Etiology and Epidemiology	Measles is caused by measles virus , a paramyxovirus with a single serotype. Transmission is by respiratory droplets . Measles virus is highly contagious, with an 85%–95% infection rate.
Clinical Manifestations	Measles has a prodromal phase characterized by fever, cough, coryza, and conjunctivitis. One to two days later, Koplik spots (small white spots on inflamed buccal mucosa) appear inside the cheek, followed a day later by a maculopapular rash, appearing first on the head and spreading to the trunk and extremities and lasting 3–5 days. Complications of measles, particularly in developing countries, in malnourished children, and in immunocompromised individuals include encephalitis, virus-induced giant-cell pneumonia, opportunistic bacterial superinfections (otitis media, pneumonia), and subacute sclerosing panencephalitis , a rare late progressive neurologic disease that occurs months or years after clinical measles.
Pathogenesis	Measles virus infects respiratory cells, spreads and multiplies in lymph nodes, and then is disseminated by viremia to distant sites including the skin and mucosa. The maculopapular rash is due to a cell-mediated immune attack on virus-infected vascular endothelial cells in the skin. Infection of T and B cells results in a depressed immune response and is the major cause of secondary infections responsible for morbidity and mortality. Cell-mediated immunity is essential to recovery from measles.
Laboratory Diagnosis	Serologic diagnosis of measles virus-specific antibody is the most common laboratory approach. RT-PCR can be used with a variety of clinical specimens.
Treatment and Prevention	There is no specific treatment for measles virus infection. Live, attenuated measles virus vaccine is highly effective in preventing measles. The vaccine is usually given in combination with mumps and rubella vaccines (MMR).

A 7-year-old white male is seen in the State Health Department clinic with fever, malaise, difficulty chewing and speaking, and salivary gland swelling and pain. His parents are migrant farm workers. There is no vaccination record. Physical examination is significant for a temperature of 38.9°C and unilateral parotitis.

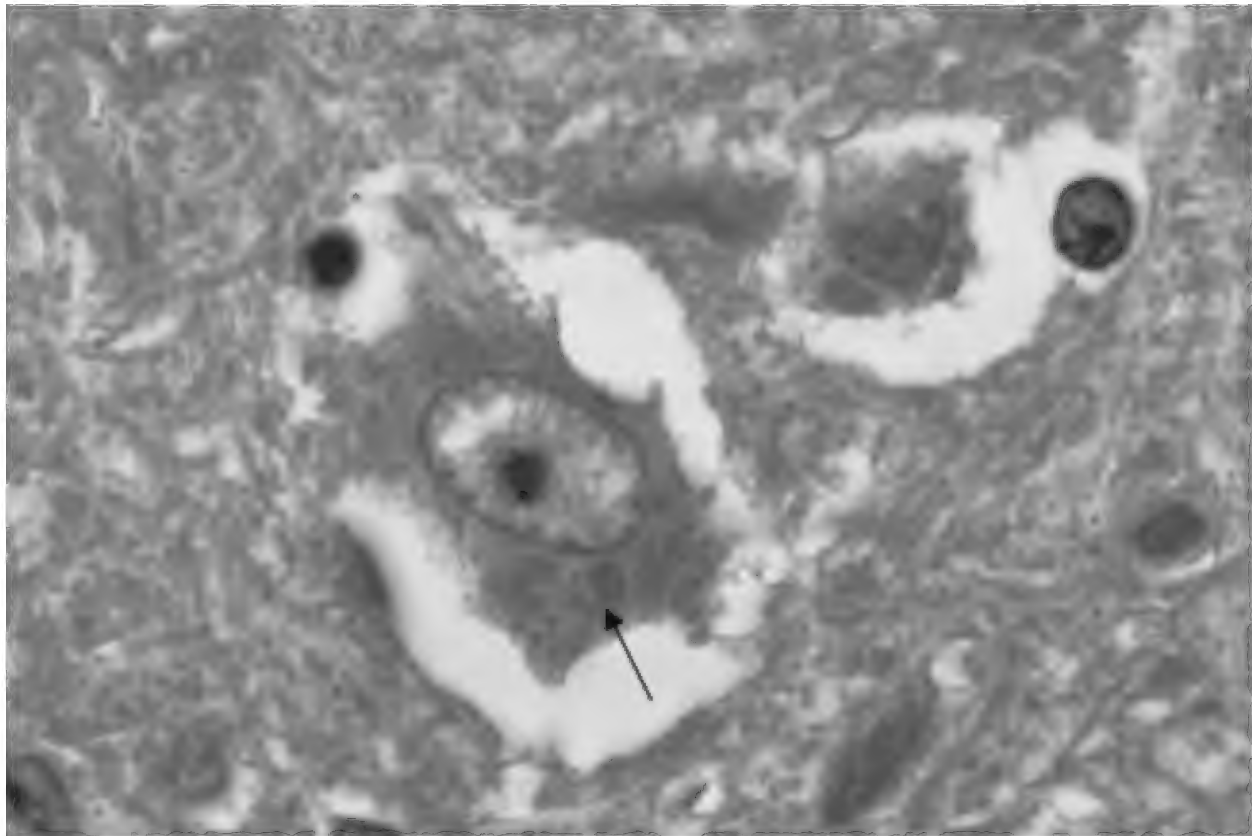


Child with salivary gland swelling. (Source: Centers for Disease Control and Prevention, Washington, DC.)

Mumps

Etiology and Epidemiology	Mumps is caused by mumps virus , a paramyxovirus with a single serotype. Mumps virus is highly contagious and transmitted by respiratory droplets, salivary secretions, or urine. Mumps is a common disease of school-age children but rare in the United States because of an effective vaccine.
Clinical Manifestations	Mumps symptoms include a prodromal phase characterized by fever, malaise, and headache followed by parotitis (parotid gland pain and inflammation and swelling). Aseptic meningitis is a common manifestation of mumps; encephalitis is rare. Complications of mumps include orchitis (inflammation/swelling of the testis) in adult males. Sterility is uncommon.
Pathogenesis	Mumps virus infects respiratory epithelial cells, spreads to regional lymph nodes, and is disseminated via viremia to the salivary glands, CNS, and other sites. Parotid gland swelling is due to inflammation, lymphocyte infiltration, and edema. Viruria (virus in the urine) is common. Cell-mediated immunity is essential to recover from disease.
Laboratory Diagnosis	Serologic diagnosis of mumps virus-specific antibody is the most common diagnostic approach.
Treatment and Prevention	There is no specific treatment for mumps virus infection. A live, attenuated mumps virus vaccine is highly effective in preventing mumps. The vaccine is usually given in combination with measles and rubella vaccines (MMR).
Notes	

A 20-year-old man is brought to the Emergency Department by his roommate because of numbness in his hand and arm, irritability, combativeness, and episodes of hyperactivity during the past week. He refuses to drink any liquids. He was bitten on the hand by a bat while trying to chase it out of his apartment about a month ago, but didn't seek medical attention.

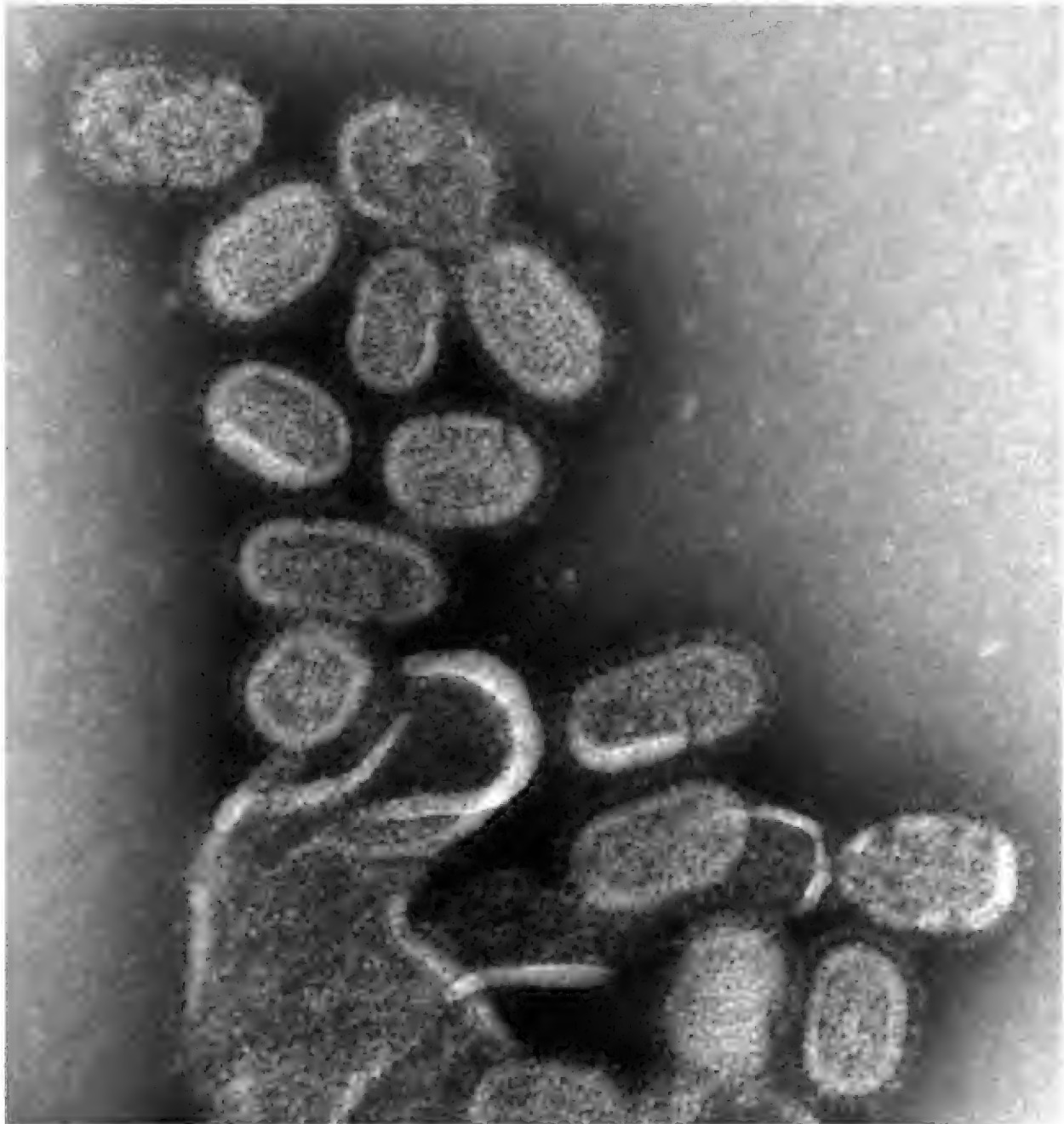


Negri body. Arrow points to Negri body, an inclusion body in cytoplasm of infected neuron. (Source: Centers for Disease Control and Prevention, Washington, DC.)

Rabies

Etiology and Epidemiology	Rabies is a viral zoonotic infection caused by rabies virus , a rhabdovirus. Rabies virus is transmitted by infectious saliva from the bite of a rabid animal, aerosol contact with mucous membranes, or (rarely) human-to-human transmission to recipients of solid-organ transplants from a rabies-infected donor. Raccoons, skunks, bats, coyotes, and foxes are natural reservoirs of infection in the United States.
Clinical Manifestations	The incubation period for rabies is variable, averaging 30–60 days after a bite exposure. A prodromal period is characterized by fever, malaise, nausea, vomiting, and pain or itching at the site of the bite wound. The neurologic phase is characterized by hyperactivity, agitation, hydrophobia, encephalitis, and coma. Rabies is almost always fatal.
Pathogenesis	Rabies virus multiplies at the site of the bite, and then infects sensory neurons by attaching to the acetylcholine receptor. The virus ascends axons to the CNS and replicates in gray matter. Virus then descends down peripheral nerves to skin and salivary glands. Cell-mediated immunity is insufficient to prevent disease.
Laboratory Diagnosis	Rabies is diagnosed by cytologic detection of Negri bodies (cytoplasmic eosinophilic inclusion-bodies) in neurons or by immunochemical detection of viral antigen in brain tissue at autopsy. In live patients, rabies virus antigens can be detected by immunocytochemistry in biopsy specimens from corneal scrapings or skin from the nape of the neck. Rabies virus RNA in saliva can be detected by RT-PCR.
Treatment and Prevention	There is no specific treatment for rabies once clinical symptoms have developed. Rabies prevention is accomplished by post-exposure and pre-exposure prophylaxis. Post-exposure prophylaxis (treatment after exposure to a bite of a rabid animal) consists of (1) thorough washing of the wound, (2) passive immunization with human rabies immune globulin into the wound, and (3) active immunization with rabies vaccine. Pre-exposure prophylaxis by active immunization with rabies vaccine is recommended for high-risk individuals (eg, veterinarians and animal handlers).

A 70-year-old woman with a history of congestive heart failure is seen in January by her primary care physician with an abrupt onset of fever, cough, and myalgias that requires hospitalization. Two days later, she experiences increasing cough and shortness of breath. Chest X-ray reveals lung infiltrates.



Electron micrograph image of virus responsible for above illness. (Source: Centers for Disease Control and Prevention, Washington, DC.)

Influenza

Etiology and Epidemiology	Influenza is caused by the orthomyxovirus influenza virus of which there are three types: A, B, and C. Influenza A can infect humans, swine, horses, and birds, and causes epidemic disease. Influenza B is limited to humans and causes a milder epidemic disease. Influenza C causes infrequent, subclinical disease. Influenza is spread by respiratory droplets . Antigenic variation of influenza virus envelope proteins— hemagglutinin (H) or neuraminidase (N) —can occur by (1) antigenic shift (influenza A only) resulting in a major change in H or N antigens or both as a result of reassortment of RNA gene segments between two influenza viruses; or (2) antigenic drift (influenza A and B) involving minor changes in H or N antigens due to point mutations. A novel H1N1 influenza caused a global pandemic in 2009. H1N1 was unusually dangerous for the young and for pregnant women, while the elderly were largely spared.
Clinical Manifestations	Influenza has an abrupt onset characterized by fever, chills, prostration, myalgias, and headache followed by respiratory symptoms of rhinitis and dry cough. Recovery is often slow with fatigue, weakness, and cough persisting for 2–4 weeks. Complications of influenza include secondary bacterial pneumonia (common) and primary viral pneumonia (uncommon). Individuals at risk of complications include the elderly and those with chronic cardiac or pulmonary disease.
Pathogenesis	Influenza virus infects respiratory epithelial cells resulting in cell death. Interferon, virus-specific secretory IgA, and cytotoxic T-cell responses are associated with recovery from infection.
Laboratory Diagnosis	Viral antigen can be detected in clinical specimens by enzyme immunoassay or immunocytochemistry. Virus can be isolated and identified in cell culture. RT-PCR is rapid, sensitive, and specific for detection of viral RNA.
Treatment and Prevention	Antiviral drugs for influenza A include amantadine and rimantadine; neuraminidase inhibitors (zanamivir, oseltamivir, and peramivir) are used for both influenza A and B. Annually updated vaccine against influenza A and B strains is the most effective method to prevent influenza and its complications.

A 55-year-old male resident of a rural area in Sudan is brought to the nearest hospital with sudden onset of fever, muscle pain, and headache followed by intense weakness, vomiting, and diarrhea. The patient was admitted to an isolation ward where his condition deteriorated with hemorrhage into the skin, mucous membranes, and internal organs. He died 12 hours later.



Electron micrograph of filovirus. (Source: Centers for Disease Control and Prevention, Washington, DC.)

Ebola Hemorrhagic Fever

Etiology and Epidemiology	Ebola and Marburg viruses are filoviruses that cause severe hemorrhagic fever . Transmission occurs by direct contact with contaminated body fluids. Ebola virus also has been found in semen of recovered patients suggesting transmission through sexual contact. The 2014–2016 Ebola outbreak in West Africa was the largest in history with 28,000 cases and 11,000 deaths. The natural reservoir for the viruses is unknown; fruit bats are a suspected reservoir.
Clinical Manifestations	Severe hemorrhagic fever is characterized by sudden onset of fever, headache, and joint and muscle pain, followed by vomiting, diarrhea, and abdominal pain. Symptoms become increasingly severe with bleeding into the skin, mucous membranes, and visceral organs. Death is due to multiorgan failure and shock.
Pathogenesis	The viruses infect macrophages and spread systemically via lymphatics and blood to infect and cause necrosis of the liver, spleen, and lymph nodes. Tissue destruction and large quantities of cytokines cause vascular permeability, hemorrhage, and shock.
Laboratory Diagnosis	Immunoassay and RT-PCR are used to detect viral antigens or viral RNA, respectively. Serology is used to detect virus-specific IgM or IgG.
Treatment and Prevention	There is no specific treatment for Ebola or Marburg hemorrhagic fever, but the 2014–2016 Ebola outbreak accelerated the evaluation of drugs that had been approved for other uses and evaluation of experimental therapies developed for treatment of Ebola virus. Experimental vaccines are under development. Isolation of patients with suspected or confirmed infections and barrier techniques are used to prevent direct contact with the patient and patient body fluids.
Notes	

A 13-year-old boy from Wisconsin was brought to the Emergency Department by his parents with complaints of fever, headache, stiff neck, malaise, nausea, and vomiting that began 2 days ago. The boy appeared disoriented and confused and had a seizure in the Emergency Department. Patient history was significant for an August camping trip in a rural, wooded area of the county 2 weeks earlier. The county health department found encephalitis-carrying mosquitoes in containers around the campgrounds.

Mosquito Control



3 Ds

- Drain** Standing water
- Dress** Cover up; wear shoes, socks, long pants, long sleeves
- DEET** Apply insect repellent

La Crosse Virus Encephalitis

Etiology and Epidemiology

La Crosse encephalitis is caused by **La Crosse virus**, a bunyavirus and a subtype of the **California encephalitis (CE) virus** serogroup. La Crosse/CE virus is an **arbovirus** and transmitted by the bite of infected *Aedes* mosquitoes. Children <16 years old are at greatest risk for La Crosse/CE. La Crosse/CE is endemic in the Midwest and is the most commonly reported arboviral encephalitis in the United States.

Clinical Manifestations

Most infections with La Crosse/CE virus are subclinical or result in mild, febrile illness. **Encephalitis** caused by La Crosse/CE virus is characterized by a sudden onset of fever, headache, malaise, nausea, and vomiting. Seizures occur in about 50% of patients with encephalitis. The disease usually resolves in 5–7 days with a case fatality rate of about 1%. Seizure disorders may be a sequela in some patients.

Pathogenesis

The bite of an infected mosquito initiates a viremia. Establishment of a secondary viremia allows dissemination of the virus to CNS target tissue. Antiviral antibody is important in viral clearance and resolution of infection, and it confers protection against reinfection.

Laboratory Diagnosis

Diagnosis is generally established by serologic testing for IgM and IgG antibodies to La Crosse/CE virus. Viral nucleic acid can be detected by RT-PCR.

Treatment and Prevention

There is no specific treatment or vaccine for La Crosse/CE viral infections. The 3Ds important in *Aedes* mosquito control are shown on the other side of this card: **Drain**: Remove or avoid standing water; **Dress**: Wear long sleeves, pants, cover the skin; **DEET**: Insecticides.

Notes

An otherwise healthy 28-year-old male biology graduate student presented to the Emergency Department with sudden onset of high-grade fever, myalgia, cough, and dyspnea. His condition deteriorated rapidly, becoming hypoxic and requiring mechanical ventilation. Chest X-ray showed evidence of bilateral

infiltrates. Patient history was significant for recently conducting field research on small mammals—including mice—in the Four Corners region of the United States.



Deer mouse. Aerosolized excreta transmits the virus. (Source: Centers for Disease Control and Prevention, Washington, DC.)

Hantavirus Pulmonary Syndrome (HPS)

Etiology and Epidemiology	Hantavirus , a bunyavirus family member, causes HPS , a viral zoonosis . Hantavirus is transmitted by Inhalation of aerosols of infected rodent deer mice, or their excreta . The deer mouse is the rodent reservoir for HPS. Person-to-person transmission of hantavirus has not been observed in the United States. Sin Nombre virus is the most important hantavirus in the United States and Canada.
Clinical Manifestations	HPS is characterized by a brief influenza-like prodromal illness consisting of fever, myalgias, headache, cough, and gastrointestinal symptoms. The disease rapidly progresses to shortness of breath, pulmonary edema, thrombocytopenia, and hypotension. The majority of patients require mechanical ventilation. HPS has a high mortality rate (>50%) in previously healthy adults.
Pathogenesis	Hantavirus multiplies in pulmonary capillary endothelial cells. At autopsy, patients with HPS had bilateral pleural effusions with interstitial infiltrates of mononuclear cells. Immune injury of virus-infected endothelial cells may be a component of HPS pathogenesis. Humoral and cell-mediated immunity are believed to be responsible for recovery and protection from repeat infection.
Laboratory Diagnosis	Diagnosis is established by serologic testing for hantavirus IgM and IgG in serum. Hantavirus antigen by immunohistochemistry or viral RNA by RT-PCR can be detected in lung tissue.
Treatment and Prevention	There is no specific treatment or vaccine for hantavirus infection. Immediate intensive care is essential once symptoms of HPS develop. Control is by avoiding close contact with infected deer mice, or their excreta.
Notes	

A 35-year-old female became ill with fever and flu-like symptoms after spending 4 months traveling on a medical mission to West Africa. Her symptoms worsened upon returning to her home in New Jersey, where she sought treatment and was hospitalized for fever (39.8°C), headache, vomiting, and diarrhea leading to severe prostration. Her condition deteriorated and she was intubated and mechanically ventilated.



Rat reservoir host for virus causing hemorrhagic fever.

Lassa Fever

Etiology and Epidemiology	Lassa fever is a viral zoonosis caused by Lassa fever virus , an arenavirus family member. Lassa virus is transmitted by aerosol inhalation or direct contact with excreta of infected rodents. Lassa fever may also spread through person-to-person contact with blood, tissue, secretions, or excretions of an infected individual. The house rat is the principal rodent reservoir. Lassa fever is endemic in West Africa. The case fatality rate is 15%–20% in hospitalized patients.
Clinical Manifestations	Lassa fever virus causes severe hemorrhagic fever characterized by fever, myalgias, and severe prostration. Hemorrhagic and CNS symptoms develop later. Hearing loss and spontaneous abortion are common complications.
Pathogenesis	Lassa virus gains entry via inhalation or skin abrasions and replicates in regional lymph nodes before producing a viremia. The virus infects macrophages and spreads systemically. Cytokine release from infected macrophages contributes to pathology and is correlated with mortality.
Laboratory Diagnosis	Serologic testing for Lassa virus-specific IgM or IgG by ELISA is the standard laboratory method for diagnosis.
Treatment and Prevention	Ribavirin is useful in the treatment of patients with severe Lassa fever. Convalescent serum, from patients who have recovered from the disease, has been found to be useful in some cases. No vaccine is available. Rodent control and strict infection control practices are important in prevention.
Notes	

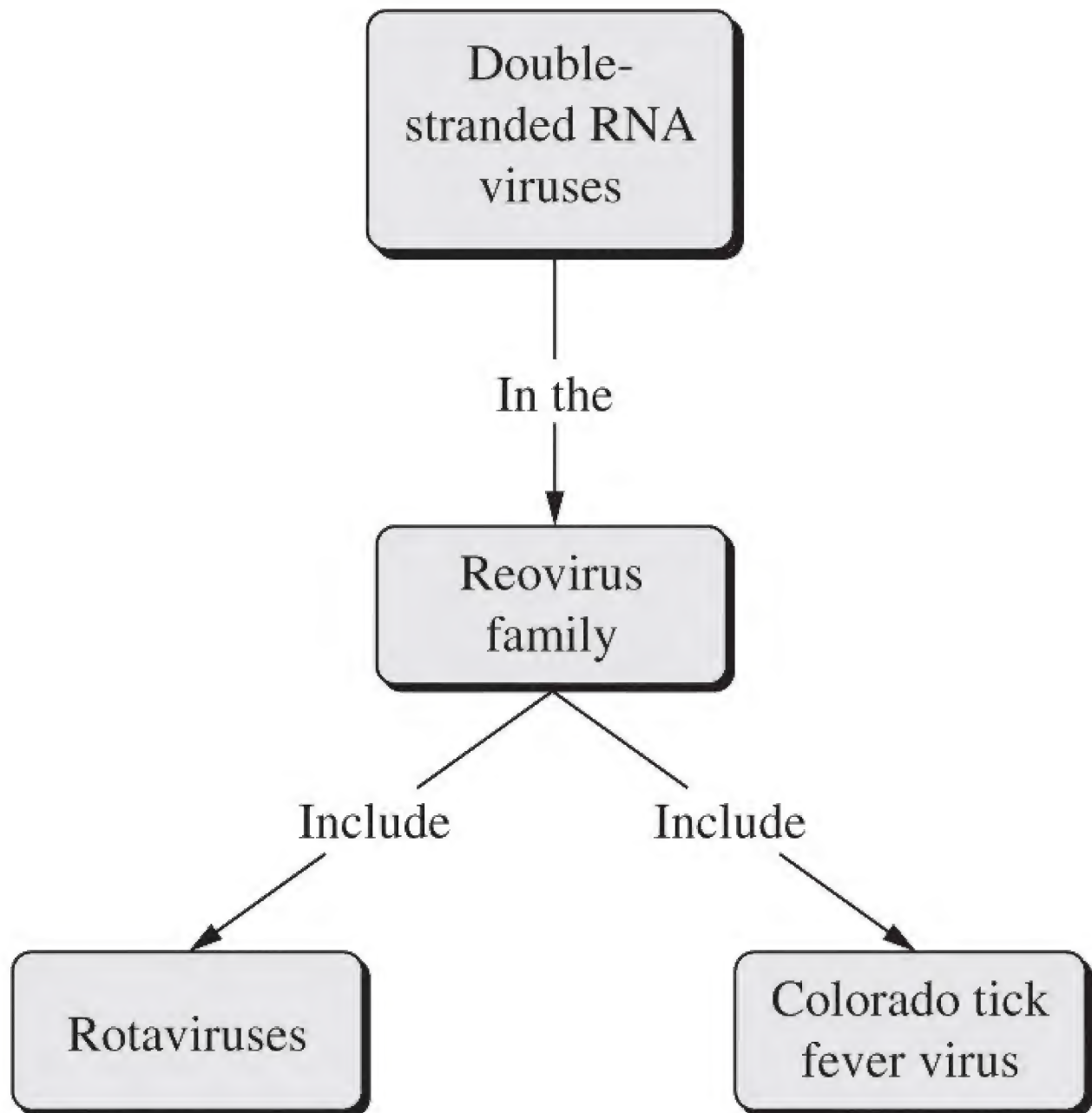
A 12-year-old boy is seen in a pediatric practice with complaints of fever, headache, myalgias, and anorexia that have lasted about a week. Clinical laboratory findings revealed lymphopenia and moderate thrombocytopenia. History of the present illness is significant for pet hamsters that he keeps in his bedroom.



Small mammal host responsible for transmission of virus via excreta.

Lymphocytic Choriomeningitis (LCM)

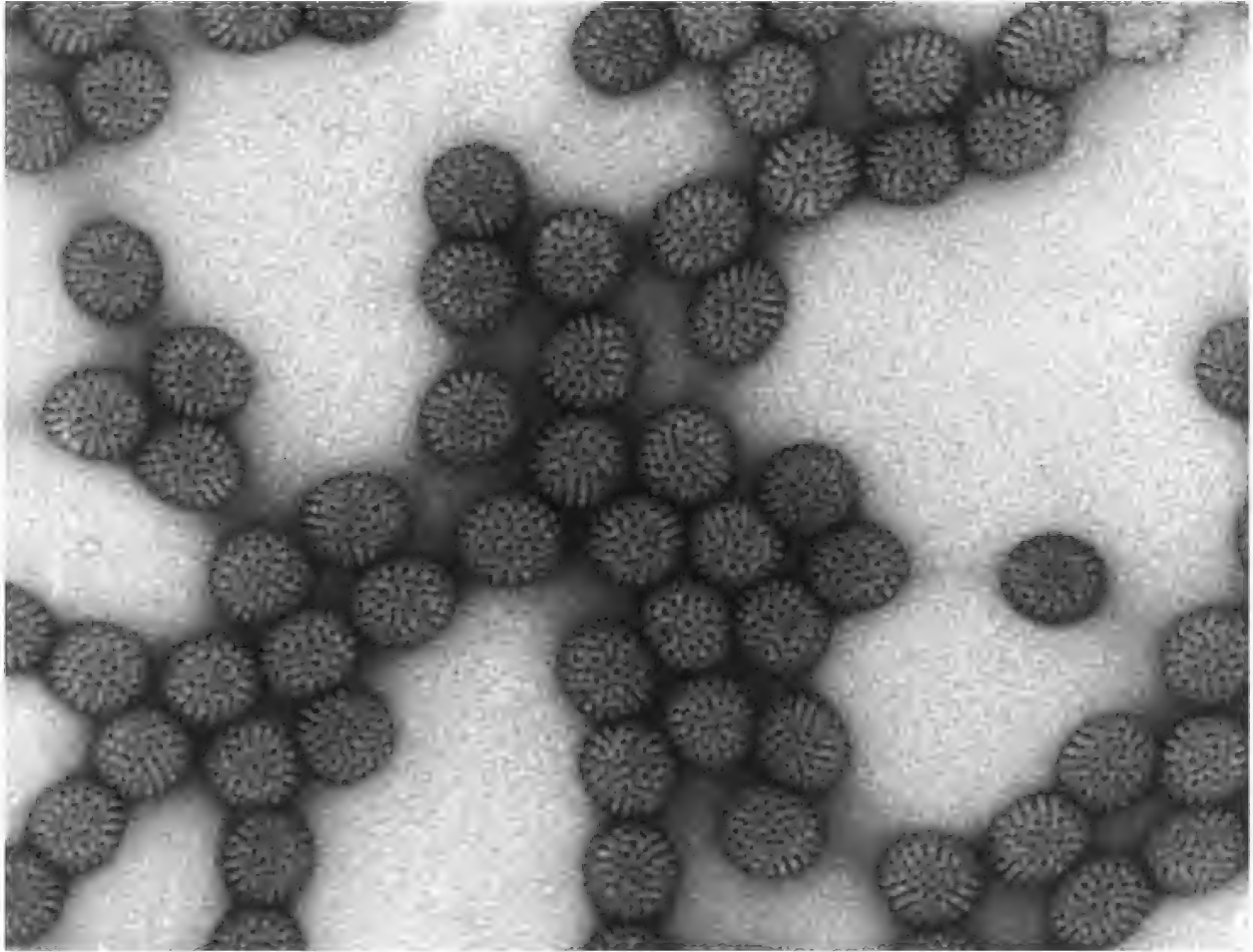
Etiology and Epidemiology	LCM is a viral zoonosis caused by LCM virus (LCMV) , an arenavirus family member. LCMV is transmitted by aerosol inhalation, ingestion of contaminated food, or exposure to secretions or excretions of infected rodents. Person-to-person transmission has not been reported with the exception of vertical transmission from an infected mother to fetus and organ transplantation from a LCMV-infected donor (rare). The house mouse and pet hamsters are common reservoirs. LCMV has a worldwide distribution and a low case fatality rate (<1%).
Clinical Manifestations	Most LCMV infections are asymptomatic. Symptomatic infections may present with an influenza-like syndrome with fever, headache, myalgias, and malaise. LCMV causes aseptic meningitis characterized by fever, headache, and stiff neck in a minority of individuals. Most patients recover completely. CNS complications such as weakness, depression, and difficulty concentrating may persist for weeks. Pregnancy-related infection has been associated with spontaneous abortion, chorioretinitis, congenital hydrocephalus, and mental retardation.
Pathogenesis	LCMV gains entry via aerosol inhalation, ingestion, or skin abrasions and replicates in lymph nodes before producing a viremia. The virus replicates in macrophages and spreads systemically. Tissue damage in meningitis is linked to release of cytokines and cytotoxic T-cell induced immunopathology.
Laboratory Diagnosis	Serologic testing for virus-specific IgM or IgG by ELISA is the routine method of diagnosis.
Treatment and Prevention	There is no specific treatment or vaccine available for LCMV infection. Rodent control is essential for prevention.



KEY CONCEPTS

- **Reoviridae** is the one family of double-stranded (ds) RNA viruses that infects humans and causes human disease.
- Reoviruses are icosahedral, nonenveloped, **segmented ds RNA** viruses that replicate in the cytoplasm.
- Reoviruses contain an **RNA-dependent RNA polymerase** as part of the virion structure.
- **Genetic reassortment** of RNA segments promoting antigenic variation is a feature of reoviruses.
- Medically important reovirus family members are **rotavirus** (11 RNA segments) and **Colorado tick fever virus (CTFV)** (12 RNA segments).

A 10-month-old infant is admitted to the pediatric unit with a 2-day history of fever, vomiting, and watery, nonbloody diarrhea. Physical examination reveals a mildly dehydrated infant with a temperature of 38.0°C but who is otherwise normal. A 3-year-old sister attends a daycare center and had a mild episode of diarrhea a week ago.



Electron micrograph image of double-shelled viral particles. (Source: Centers for Disease Control and Prevention, Washington, DC.)

Gastroenteritis

Etiology and Epidemiology	Rotaviruses are the single most important cause of gastroenteritis in infants and young children. Rotaviruses are transmitted by the fecal-oral route. Infection occurs worldwide with an estimated 1 million infant deaths due to severe diarrhea, particularly in developing countries. Rotavirus gastroenteritis occurs in all age groups, with the peak incidence of severe illness in children 6–24 months of age.
Clinical Manifestations	Rotavirus infection is characterized by the sudden onset of nausea, low-grade fever, vomiting, and nonbloody, watery diarrhea lasting 4–5 days. Dehydration and electrolyte loss are major complications of severe diarrhea. Patients with malnutrition and associated immunodeficiencies are at an increased risk of developing severe rotavirus infections.
Pathogenesis	After ingestion, rotaviruses infect and lyse epithelial cells (enterocytes) of the small intestine. Damaged enterocytes subsequently slough, resulting in stunted villi. Damage to enterocytes is associated with a flux of extraintestinal fluid across the intestinal membrane, resulting in net sodium and protein loss in some patients. Mucosal injury results in a decreased absorptive surface area of the small intestine and decreased production of digestive enzymes (eg, disaccharidases). These deficiencies result in a malabsorptive state leading to a hyperosmotic effect that causes diarrhea. Viral clearance and subsequent immunity are correlated with serum antibody. Intestinal secretory IgA response is correlated with immunity to reinfection.
Laboratory Diagnosis	Detection of rotavirus antigen in stool by enzyme immunoassay is the method routinely used for diagnosis of infection.
Treatment and Prevention	There is no specific therapy for rotavirus infection. Oral rehydration is required in severe cases to replace fluids and electrolytes. Two live, attenuated, oral rotavirus vaccines are licensed for use in the United States to prevent rotavirus diarrhea in infants. Improved sanitation measures and good hygiene are methods of control.

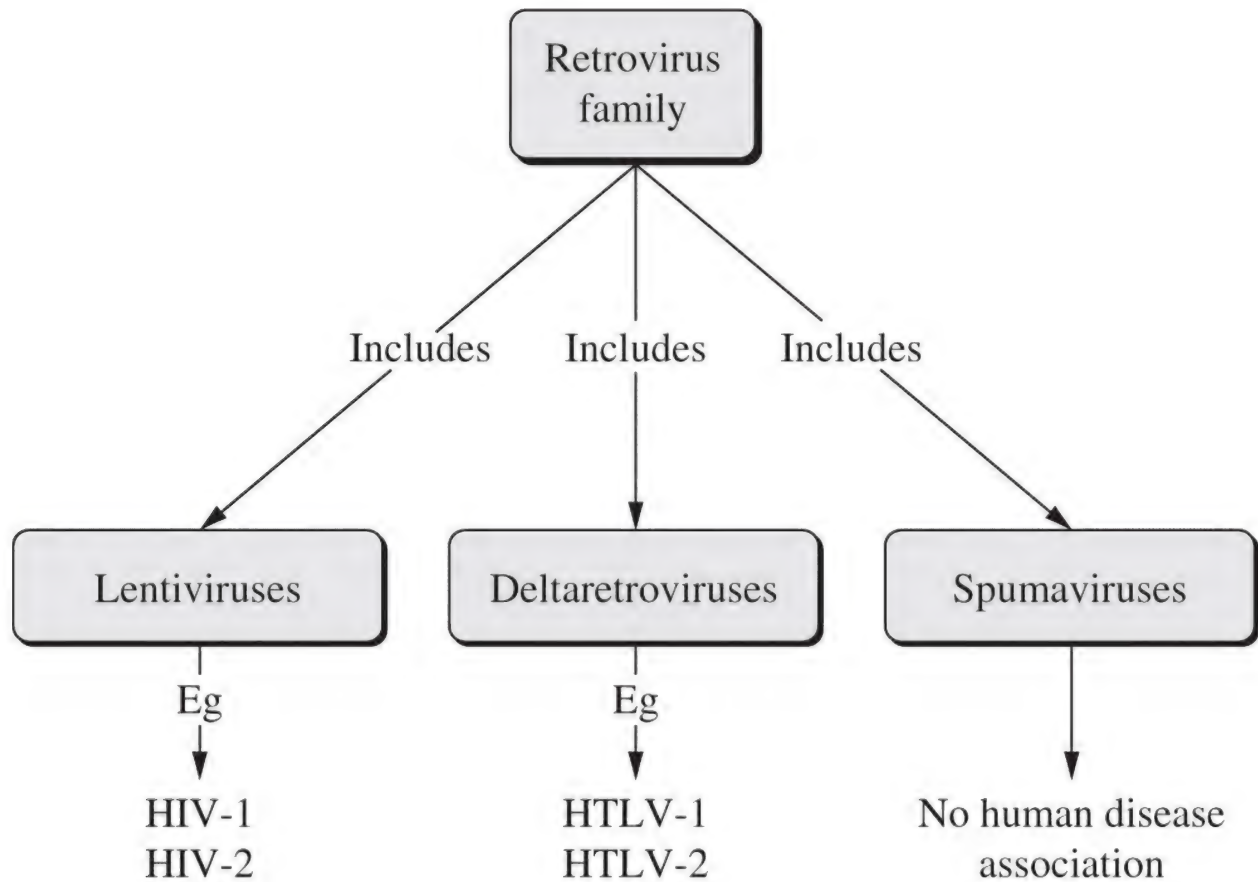
A 40-year-old businessman is seen in the Emergency Department with fever, chills, headache, muscle aches, abdominal pain, and vomiting. He returned the previous week from a hiking trip in Utah and reported being bitten by a tick. He is admitted to the hospital, where his temperature cycles from febrile to afebrile over the next several days. Laboratory findings of significance are a moderate leukopenia and thrombocytopenia.



Wood tick: Vector in viral zoonosis. (Source: Centers for Disease Control and Prevention, Washington, DC.)

Colorado Tick Fever

Etiology and Epidemiology	Colorado tick fever is a viral zoonosis caused by Colorado tick fever virus (CTFV) . CTFV is an arbovirus transmitted by the bite of an infected wood tick , <i>Dermacentor andersoni</i> . CTFV is endemic throughout the western United States. The natural reservoir for CTFV is small mammals (eg, squirrels, chipmunks).
Clinical Manifestations	CTFV infection causes an acute febrile illness characterized by fever, myalgia, chills, headache, malaise, abdominal pain, and vomiting. A “saddle-back” fever pattern, consisting of a 2–3 day febrile period followed by an afebrile period and subsequent return of the fever, is seen in approximately half of affected patients. Encephalitis or hemorrhagic fever is a complication of CTFV infection, especially in children. Fatalities are rare.
Pathogenesis	CTFV enters the skin via a tick bite and infects and replicates in hematopoietic cells, including erythrocyte precursors. Direct cytopathic effects of the virus on stem cells are likely to account for the frequently observed leukopenia and thrombocytopenia. The virus persists in mature erythrocytes masked from immune clearance. Recovery is associated with elevated levels of neutralizing antibody and immunity to reinfection.
Laboratory Diagnosis	CTFV antigens can be detected on the surface of erythrocytes by direct immunostaining of blood smears. Serologic testing for virus-specific IgM or IgG by enzyme immunoassay can be used for diagnosis of CTFV infection.
Treatment and Prevention	There is no specific therapy or vaccine for CTFV. Protection from ticks, especially in endemic areas, is the best control method.



KEY CONCEPTS

- A virion-associated **reverse transcriptase (RT)** RNA-dependent DNA polymerase is the hallmark of retroviruses.
- Retroviruses establish persistent lifelong infections.
- Medically important members of the **Retroviridae** family are the

lentiviruses, which include **HIV-1 and HIV-2**; and the **deltaretroviruses**, which include **human T-cell lymphotropic virus 1 and 2 (HTLV-1 and 2)**. One other family member (Spumavirus) is not associated with human disease.

- HIV-1 and 2 lentiviruses are **cytopathic** and destroy target cells.
- HTLV-1 and 2 delta retroviruses are not cytolytic but are **transforming** and capable of cell immortalization, leading to malignancy.
- HIV-2 is of lower virulence than HIV-1, and infection is largely confined to West Africa.
- HTLV-2 disease association remains uncertain.

A 40-year-old male is seen by his internist with chief complaints of fever, night sweats, increased episodes of diarrhea during the past month, and a 30-pound weight loss over the previous 4 months. On physical exam, he has oral thrush and cervical lymphadenopathy. Laboratory findings are significant for a CD4+ cell count of 30 cells/mL.

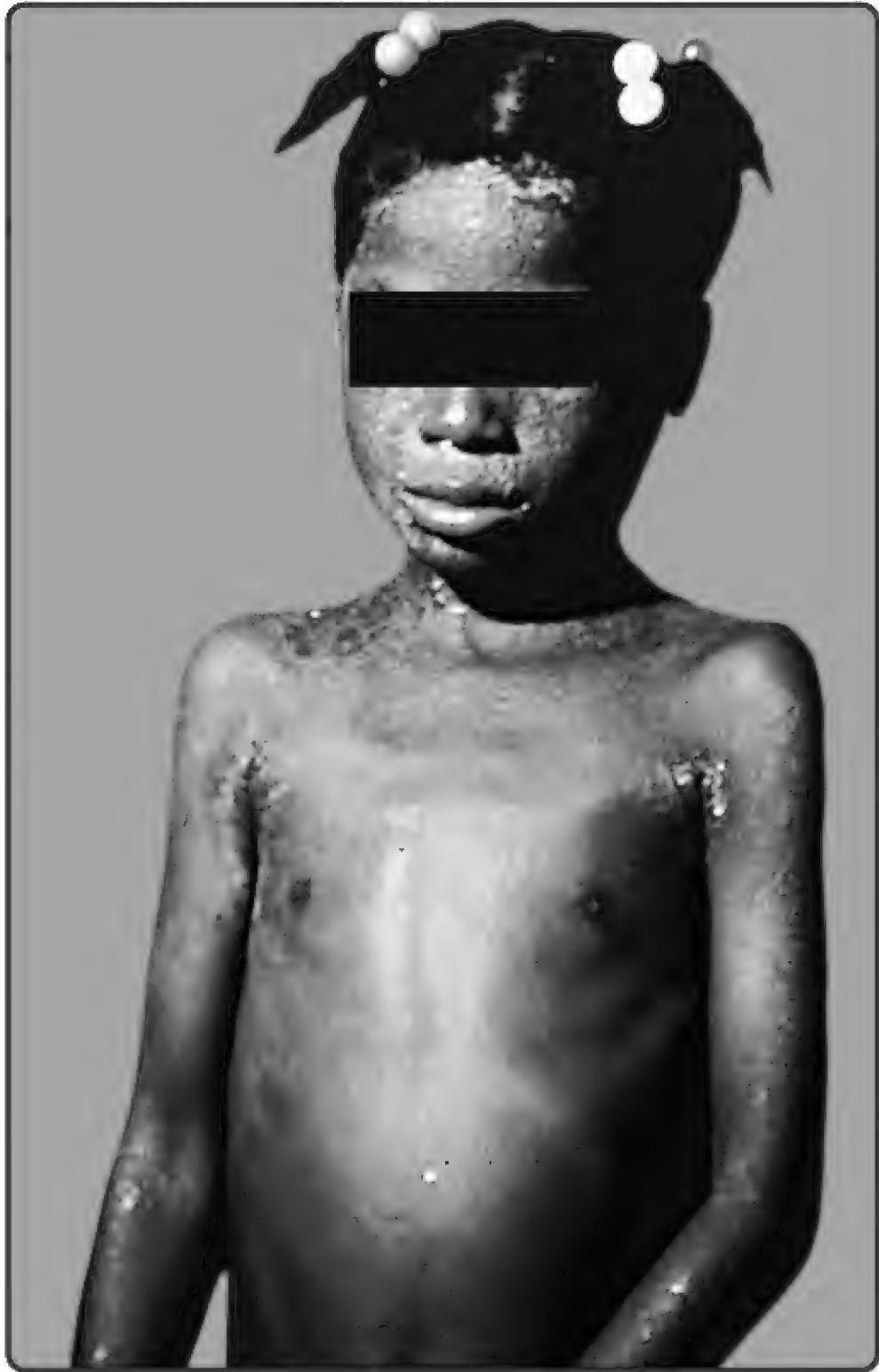


Oral thrush caused by *Candida albicans*. (Source: Centers for Disease Control and Prevention, Washington, DC.)

HIV/AIDS

Etiology and Epidemiology	HIV-1 causes AIDS . A second type, HIV-2, has remained largely confined to West Africa, whereas HIV-1 has spread worldwide. HIV-1 is transmitted by sexual contact, blood, intravenous drug use, and from infected mother to child either transplacentally or perinatally. Contact among homosexual and bisexual men is the major mode of HIV-1 transmission in the United States. Heterosexual transmission is most common in the rest of the world.
Clinical Manifestations	HIV disease is characterized by an acute phase with a “flu-like” or infectious mononucleosis-like syndrome, followed by an asymptomatic phase of clinical latency characterized by fatigue, weight loss, night sweats, or lymphadenopathy with a median time of 10 years to development of AIDS. AIDS is defined by a CD4+ T lymphocyte count <200/mL (normal = 800–1200/mL) or the presence of an AIDS-defining condition such as opportunistic protozoal, fungal, bacterial, and viral infections or certain, associated malignancies (eg, Kaposi sarcoma), regardless of the CD4+ cell count.
Pathogenesis	HIV-1 attaches via the envelope glycoprotein gp120 to the CD4 molecule and a second co-receptor (chemokine receptor, CCR5 or CXCR4) on helper T lymphocytes, monocytes-macrophages, and mucosal dendritic cells. HIV-1 may infect both activated and nonactivated CD4+ cells in the draining lymph node. Virus remains latent in nonactivated (resting) T cells but replicates in and kills T cells activated by infection, cytokines, or both.
Laboratory Diagnosis	HIV and AIDS are diagnosed by the detection of virus-specific antibodies to HIV-1 (screening test) and confirmed by Western blot assay. RT-PCR is used to quantitate the amount of HIV-1 in plasma (viral load) and is used, along with the CD4+ cell count, to monitor disease progression and response to antiretroviral therapy.
Treatment and Prevention	Treatment involves combination therapy of at least three agents selected from multiple classes of antiretroviral drugs. Six major classes of HIV antiretroviral agents currently exist (see Chapter 12): NRTIs, NNRTIs, PIs, INSTIs, fusion inhibitor, and CCR5 antagonist. An appropriate and effective combination regimen is referred to as highly active antiretroviral therapy (HAART) . Post exposure prophylaxis with antiretroviral drugs for occupational and nonoccupational exposures can be given within 72 hours of exposure. There is no vaccine to prevent HIV-1 infection. Screening of blood for HIV-1 antibody has prevented HIV transmission by blood transfusion. Maternal–infant transmission of HIV-1 can be reduced significantly by antiretroviral therapy for the pregnant mother and newborn infant.

A 60-year-old male is seen by his physician with complaints of a persistent skin rash, fatigue, swollen glands in the groin and under the arms, and a distended abdomen. He is an immigrant from Jamaica in the Caribbean Islands. Physical exam reveals an enlarged liver and spleen and extensive skin rashes. Laboratory findings demonstrate a marked lymphocytosis with pleiotropic features, elevated LDH, and hypercalcemia.



HTLV-1 Adult T-Cell Leukemia

Etiology and Epidemiology	The retrovirus HTLV-1 is the causative agent of adult T-cell leukemia (ATL) and a neurologic disorder called HTLV-1-associated myelopathy-tropical spastic paraparesis (HAM-TSP) . Endemic foci exist in the Caribbean, Japan, India, West and Central Africa, South America and Papua New Guinea. HTLV-1 is highly cell-associated and transmitted primarily by HTLV-1-infected cells, not virus particles per se. HTLV-1 is transmitted between individuals by transfer of infected lymphocytes in breast milk, semen, and blood.
Clinical Manifestations	ATL is characterized by a long asymptomatic incubation period of 20–50 years, increased numbers of leukemia cells, skin lesions, systemic lymphadenopathy, hepatosplenomegaly, and hypercalcemia. The lifetime risk for development of ATL in an infected individual is 3%–5%. HAM-TSP is characterized by a shorter incubation period (2–4 years) than ATL, demyelination of the long motor neurons of the spinal cord, muscle weakness in the legs, progressive spasticity, back pain, urinary incontinence, hyperreflexia, sensory disturbances, and impotence in men. The lifetime risk for development of HAM-TSP is ~1%.
Pathogenesis	HTLV-1 infects primarily CD4+ T lymphocytes. HTLV-1 encoded regulatory protein Tax stimulates the growth and mitogenesis of CD4+ T cells by inducing cellular transcription factors that activate cellular growth factors and growth factor receptors (eg, interleukin-2 [IL-2] and IL-2 receptor). HAM-TSP pathogenesis is characterized by a CNS infiltration of HTLV-1 infected lymphocytes and a marked cytotoxic lymphocyte response with collateral damage to neurologic tissues.
Laboratory Diagnosis	HTLV-1 infection is detected by EIA for virus-specific antibody.
Treatment and Prevention	There is no specific treatment or vaccine for HTLV-1. Screening of blood can prevent transfusion-associated transmission of HTLV-1 and elimination of breastfeeding by HTLV-1 infected mothers would prevent maternal-infant transmission. Prevention measures established for HIV infection are applicable for HTLV-1.
Notes	

SLOW INFECTIONS CAUSED BY CONVENTIONAL VIRUSES AND PRIONS

Disease	Host	Virus/Agent	Brain Lesion
Conventional Viruses			
Subacute sclerosing panencephalitis (SSPE)	Human	Defective measles virus	Demyelination, inflammation
Progressive multifocal leukoencephalopathy (PML)	Human	JC polyomavirus	Demyelination, inflammation
Prions			
Kuru	Human	Prion	TSE
Creutzfeldt-Jakob disease (CJD)	Human	Prion	Spongiform encephalopathy (SE) characterized by sponge-like lesions of the brain leading to neuronal loss without inflammation.
Gerstmann-Sträussler-Scheinker disease (GSS)	Human	Prion	TSE
Fatal familial insomnia (FFI)	Human	Prion	TSE
Bovine spongiform encephalopathy (BSE)	Cattle	Prion	TSE
Scrapie	Sheep and goats	Prion	TSE
Chronic wasting disease	Mule deer and elk	Prion	SE

SE, spongiform encephalopathy

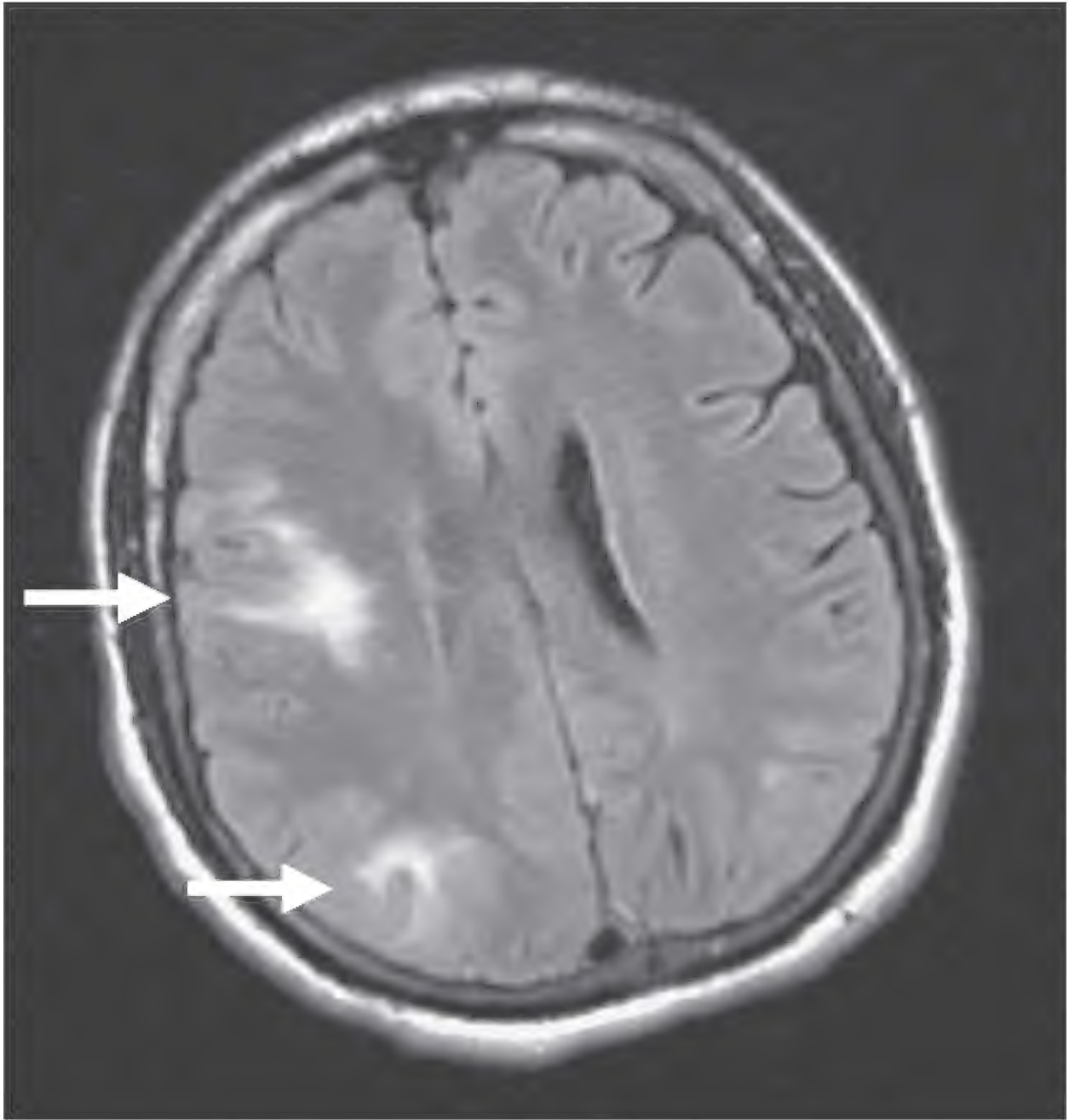
KEY CONCEPTS

- Slow infections include a group of diseases that have a prolonged incubation period (months to years) and a slowly progressive clinical course ending in death.
- The protracted course of slow infections requires that the causative agent be

able to evade host defenses and establish a persistent infection.

- Central nervous system involvement is a hallmark of slow infections. The CNS sequesters the infectious agent and functions as a sanctuary.
- Slow infections are classified as
 - ▶ Diseases associated with conventional viruses.
 - ▶ Diseases associated with unconventional, infectious proteins known as **prions**.
- Medically important slow virus diseases caused by conventional viruses are **progressive multifocal leukoencephalopathy (PML)** and **subacute sclerosing panencephalitis (SSPE)**.
- Medically important slow diseases caused by prions are the **transmissible spongiform encephalopathies**.

A 34-year-old male presents to the Emergency Department with a progressive gait disorder of about 2 months. The patient is concerned that he might have multiple sclerosis. A series of laboratory tests are ordered that prove to be either negative or within normal limits. His condition gets progressively worse over the next few weeks. An MRI is ordered and reveals patchy lesions in the white matter of the brain. Past medical history is significant for an HIV+ enzyme immunoassay, a CD4 count of 10, and a viral load of 500,000. The patient had previously declined treatment with highly active antiretroviral therapy (HAART) when he was diagnosed with HIV/AIDS.



MRI of progressive multifocal leukoencephalopathy. Note high signal intensity (arrows) in white matter. (Reproduced, with permission, from Aminoff MJ, Greenberg D, Simon RP. *Clinical Neurology*. 9th ed. New York: McGraw-Hill; 2016.)

Progressive Multifocal Leukoencephalopathy (PML)

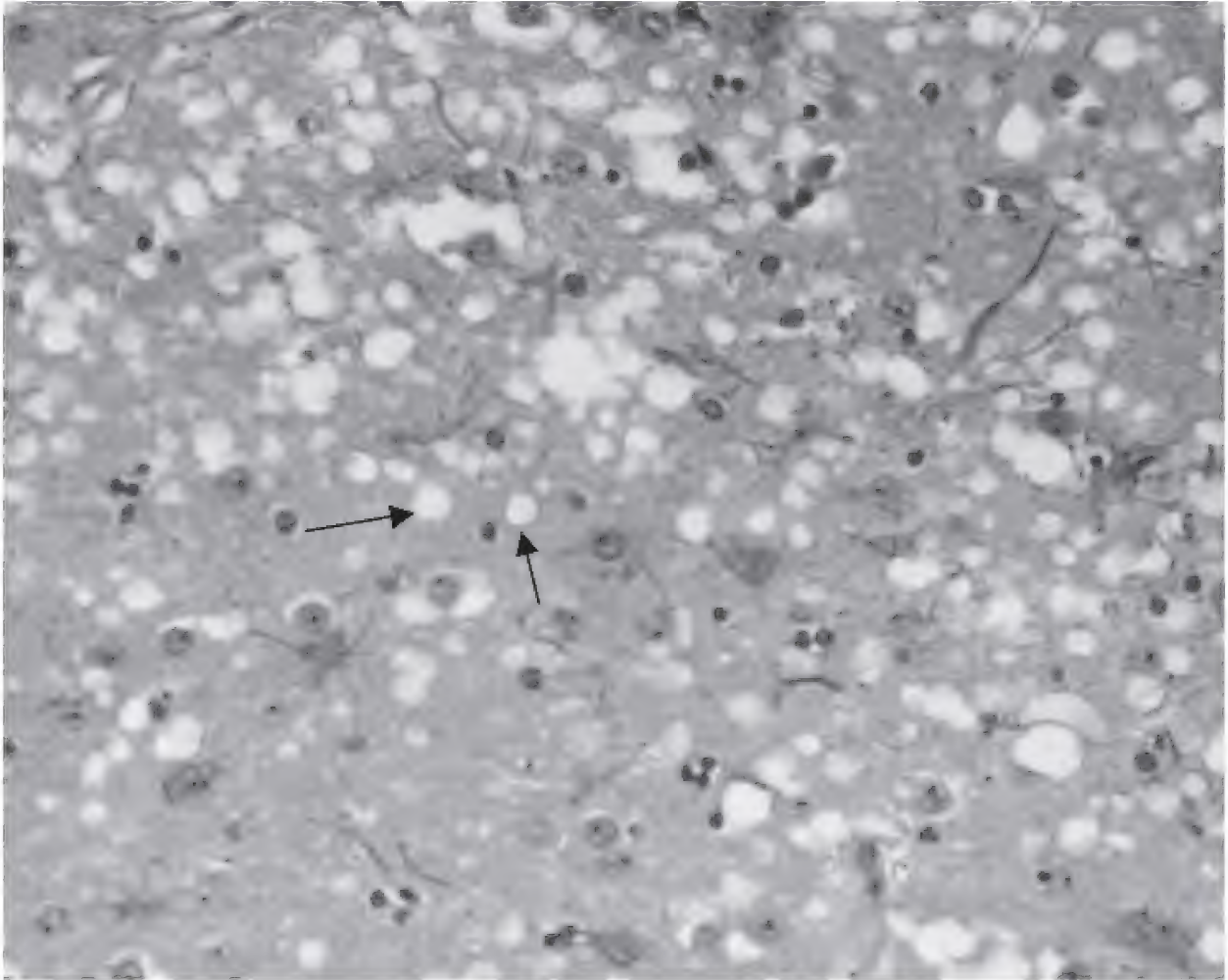
Etiology and Epidemiology	PML is caused by the human polyomavirus, JC virus (JCV) . JCV is transmitted by respiratory tract droplets , occurs early in childhood, and reaches a seroprevalence of 70%–80% in adults. Latent infections are reactivated in severely immunosuppressed patients.
Clinical Manifestations	PML is a demyelinating disease of the brain usually in adults with immunosuppressive diseases, particularly in patients with HIV/AIDS although it can infrequently occur in some patients with myeloproliferative or lymphoproliferative diseases or even more rarely, in patients receiving immunomodulatory agents. Disease onset is insidious. Early signs include speech and vision abnormalities and alteration of mental function. The clinical course of PML is progressive, culminating in coma and death, usually within 6 months of onset.
Pathogenesis	JCV is likely acquired via the respiratory route and spread by viremia to establish latent infection in the kidneys, lungs, and lymphoid organs. In immunocompromised individuals, JCV is activated, spreads to the brain, and causes PML. In the CNS, JCV attaches to the serotonin receptor on oligodendrocytes and causes a lytic infection. Oligodendrocytes are the major myelin-producing cell in the CNS. The mechanism of immune evasion by JCV is opportunism in the immunosuppressed patient.
Laboratory Diagnosis	JCV infection can be detected by PCR in the CSF or in brain biopsy specimens from patients with PML.
Treatment and Prevention	There is no specific treatment or vaccine for PML.
Notes	PML is an AIDS-defining illness.

A 12-year-old boy is brought to the Emergency Department after wandering in the street, apparently confused after falling off his bike. His parents report that he had been developing normally up to 10 years of age, when his teachers began noticing personality changes and progressive deterioration in his schoolwork. Screening tests for alcohol and recreational drugs are negative. Serologic results for CMV and HIV are negative. Anti-measles antibody titers are 640 in serum and 5120 in CSF.

Subacute Sclerosing Panencephalitis (SSPE)

Etiology and Epidemiology	A defective measles virus mutant is the cause of SSPE. Measles virus is transmitted by respiratory droplets. SSPE is a rare, late progressive neurologic disease of children with the majority of cases appearing 6–8 years after acute measles. Incidence of SSPE in unvaccinated children is 1 in 1 million cases.
Clinical Manifestations	SSPE is characterized by an insidious onset of personality changes, intellectual deterioration, with later myoclonic jerks (periodic muscle spasms), spasticity, blindness, and death. The clinical course is progressive, with death occurring 1–3 years after onset.
Pathogenesis	Brain pathology in SSPE consists of demyelination and inflammation due to chronic infection by SSPE measles virus over the course of years. Measles virus defective in virion production can be isolated from brain cells of patients with SSPE. The measles virus variant that causes SSPE has mutations in the matrix (M) protein responsible for viral assembly and budding. The lack of a functional M protein results in nonproductive infection by SSPE measles virus. Patients with SSPE have elevated levels of measles virus antibodies in serum and CSF, but no antibody to the M protein. Measles virus escapes immune surveillance by cell-to-cell fusion mediated by the fusion (F) protein.
Laboratory Diagnosis	Patients with SSPE are diagnosed by the detection of high measles virus antibody titers in serum and CSF.
Treatment and Prevention	There is no specific treatment for measles virus infection. Live, attenuated measles virus vaccine is highly effective in preventing measles and has markedly reduced the incidence of SSPE.
Notes	

A 67-year-old previously healthy woman was referred to a neurologist because of a 2-month history of increased dementia manifested as confusion, memory loss, and bizarre behavior. On physical examination, she exhibited ataxia, slurred speech, and myoclonic jerking movements of the extremities. Hematologic studies, clinical chemistries, and a brain MRI were normal.



Spongiform encephalopathy in prion disease. Arrows point to spongiform appearance (Swiss cheese-like holes) in the brain.

Creutzfeldt-Jakob Disease (CJD)

Etiology and Epidemiology	CJD is a rare disease (1 case per million people) caused by infectious proteins termed prions . Sporadic CJD accounts for most cases (85%); 10%–15% of CJD cases are familial. Iatrogenic transmission of CJD has been detected after transplantation of contaminated corneal grafts, dura mater grafts, or injection of human pituitary-derived growth hormone and the use of contaminated medical devices (brain electrodes) incompletely sterilized between patients. New variant CJD is acquired by ingestion of bovine spongiform encephalopathy-contaminated beef and can be transmitted between humans by blood transfusion.
Clinical Manifestations	CJD is a progressive, neurodegenerative disease with onset usually between ages 50–70 years. CJD is characterized clinically by dementia, myoclonus (involuntary movements), and ataxia. The disease progresses to severe dementia and death within 6 months to 1 year.
Pathogenesis	Prion diseases are believed to occur from the accumulation in neurons of a protease-resistant isoform of a normal cellular protein (prion protein, PrP ^c) that has an altered conformation and is designated as PrP ^{sc} . The “misfolded” PrP ^{sc} binds normal PrP ^c and acts as a template to induce a conformational change in PrP ^c , converting it into the abnormal misfolded PrP ^{sc} form. The process continues in a cascade-like fashion until abnormal PrP ^{sc} accumulates to levels associated with neuronal dysfunction and neuronal death. Accumulation of PrP ^{sc} in the brain is the pathognomonic feature with the formation of amyloid-like fibrils and plaques. Extensive vacuolation, neuronal loss, and gliosis are also seen by pathology. Prions escape immune surveillance because they are nonantigenic host proteins.
Laboratory Diagnosis	Histopathological examination of brain sections at autopsy shows characteristic spongiform changes characterized by a “spongy” appearance (holes in the tissue). Immunohistochemistry with anti-prion antibody is used to stain brain specimens.
Treatment and Prevention	There is no specific treatment and no immunologic approaches to prevent prion diseases.

PROPERTIES OF FUNGI

- Fungi are eukaryotic organisms and have a true nucleus (ie, surrounded by a nuclear membrane), unlike prokaryotic bacteria.
- Fungi are not photosynthetic and lack chlorophyll.
- Fungi secrete enzymes that digest plant and animal tissue and utilize the soluble nutrients for growth.

STRUCTURE

- Fungal cells are composed of
 - ▶ A **plasmalemma** (or **cell membrane**) that is composed of glycoproteins, lipids, and **ergosterol**, which encloses the cytoplasm.
 - ▶ The rigid **cell wall** exterior to the plasmalemma is composed of **chitin**, an unbranched polymer of N-acetylglucosamine; **glucans**, which are glucose polymers; and **mannans**, polymers of mannose. These components are cross-linked to form a multilayered cell wall complex.
 - ▶ Species-specific polysaccharides may also be present and therefore useful for identification.

GROWTH

- Fungi can be grouped morphologically as either **yeasts** (single cells that reproduce by budding) or **molds** (multicellular, filamentous forms of fungi composed of threadlike, branching filaments termed **hyphae** that form an intertwined mass called the **mycelium** or mold).
- Hyphae may have cross walls (**septa**) or not. These structural features aid in identification (ie, **septate** or **nonseptate**).
- Some fungi are **dimorphic** and can exist as either a hyphal form or a yeast

form under different growth conditions (e.g., in vitro at 25 °C versus in vivo at 37 °C).

- Fungi can reproduce either asexually or sexually by the formation of **spores**, specialized structures for dissemination and survival under adverse conditions.
- The medically important fungi produce two major types of spores: **conidia** and **sporangiospores**.
 - ▶ Conidia are produced by most pathogenic fungi. They are formed externally by mitosis on a specialized hyphal structure called the **conidiophore**. **Macroconidia** and **microconidia** denote the size and complexity of conidia.
 - ▶ Sporangiospores are a characteristic of the order Mucorales. They are mitogenic spores produced internally within specialized structures termed sporangia.

FUNGAL PATHOGENESIS AND HOST RESPONSE

- Mechanisms of fungal pathogenesis are poorly understood.
- Fungal surface mannoproteins mediate adherence to target cells in some species of fungi.
- Most human fungal infections are relatively mild and self-limited because of a high level of innate immunity to fungi.
- Progressive and life-threatening fungal diseases are a common theme in immunocompromised patients.
- Host resistance is due to the fatty acid content, pH, epithelial cell turnover, and normal bacterial flora of the skin, as well as the pH of mucosal surfaces and cilia of the respiratory tract.
- Host responses to systemic fungal infections can result in the formation of granulomas, which are characterized by an inflammatory cell infiltrate with macrophages that phagocytize fungi, resulting in a localized nodule that serves to contain the infection.
- Neutrophils phagocytize and kill fungi. Capsular polysaccharides of some fungi are antiphagocytic.
- T-cell-mediated immunity is a key determinant in protection from disease.
- Fungal mannoproteins elicit strong T- and B-cell immune responses.

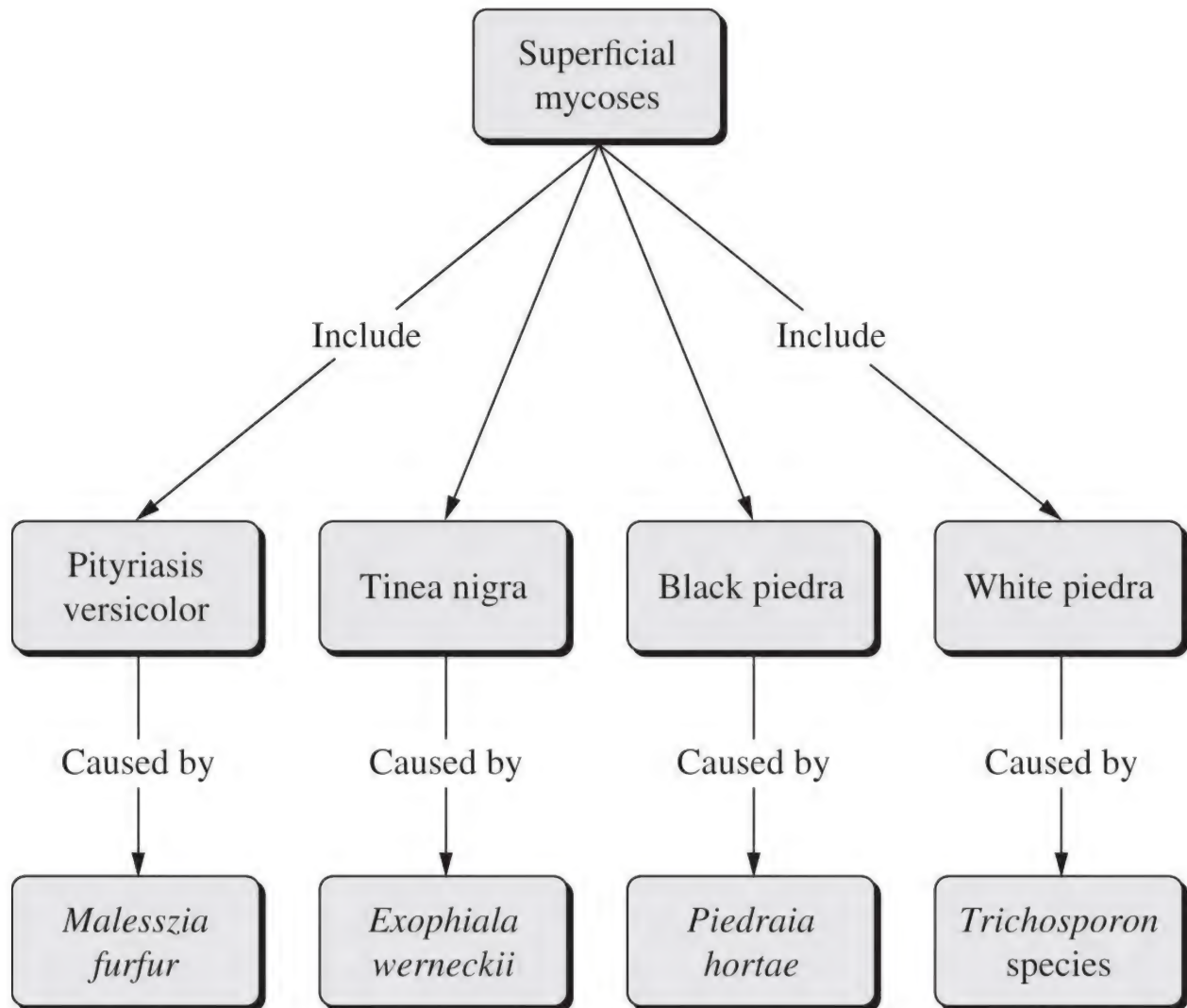
LABORATORY DIAGNOSIS

- Detection and identification of fungi can be made by culture and nonculture methods.
- Sabouraud's medium, commonly used to culture fungi, is selective for fungal growth because of acid pH and high sugar content.
- Nonculture methods include direct microscopic examination, antigen detection by enzyme immunoassay or latex agglutination, and nucleic acid detection by PCR.
- Gomori methenamine silver stain and periodic acid-Schiff stain are special stains used to detect yeast cells and hyphae in tissues.
- Clinical specimens, treated with 10% potassium hydroxide (KOH) to digest tissue material but leave fungal cell walls intact, are examined microscopically as wet mounts to detect fungi.

PROPERTIES OF SELECTED ANTIFUNGAL AGENTS

Agent	Mode of Action	Treatment	Clinical Use
Griseofulvin (grisan)	Disrupts microtubules; mitotic poison	Systemic	Dermatophytes
Amphotericin B (AmB) (polyene)	Binds to ergosterol & disrupts membrane integrity	Systemic	Most fungi
Liposomal AmB (polyene)	Same as AmB	Systemic	Most fungi; less toxic than AmB
Nystatin (polyene)	Same as AmB	Topical	<i>Candida spp</i>
Fluconazole (triazole)	Targets lanosterol demethylase, part of the ergosterol biosynthesis pathway	Systemic	<i>Candida spp</i> <i>Cryptococcus spp</i>
Itraconazole (triazole)	Same as fluconazole	Systemic	<i>Candida spp</i> , <i>Aspergillus spp</i> <i>Sporothrix schenckii</i> , <i>Histoplasma capsulatum</i> , <i>Blastomyces dermatitidis</i>
Voriconazole (extended-spectrum triazole)	Same as fluconazole	Systemic	<i>Candida spp</i> , <i>Aspergillus spp</i> , <i>Fusarium spp</i> , <i>Scedosporium spp</i>
Posaconazole (extended-spectrum triazole)	Same as fluconazole	Systemic	<i>Aspergillus spp</i> , <i>Mucor spp</i> , <i>Coccidioides immitis</i> , <i>Candida spp</i>

Isavuconazole (extended-spectrum triazole)—approved by U.S. Food & Drug Administration (FDA) in 2015	Same as fluconazole	Systemic	Spectrum of activity similar to that of voriconazole and posaconazole; currently FDA approved for treatment of invasive aspergillosis and mucormycosis
Miconazole, clotrimazole (topical imidazoles)	Same as fluconazole	Topical	Vulvovaginal candidiasis and candidal yeast infections of skin
Ketoconazole (imidazole)	Same as fluconazole	Topical (systemic use avoided due to poor bioavailability, significant drug toxicity, and drug-drug interactions)	<i>Candida spp.</i> , Dermatophytes, <i>Malassezia furfur</i> , some dimorphic fungi (such as <i>Blastomyces dermatitidis</i>)
5-Fluorocytosine (Flucytosine) (nucleoside analogue)	Inhibits RNA and DNA synthesis	Systemic	<i>Candida spp.</i> , <i>Cryptococcus spp.</i>
Terbinafine (allylamine)	Inhibits ergosterol biosynthesis via inhibition of squalene epoxidase	Systemic, topical	Dermatophytes; especially onychomycosis
Caspofungin, micafungin, anidulafungin (echinocandins)	Inhibits cell wall (1,3)- β -D-glucan synthesis	Systemic	<i>Candida spp.</i> , <i>Aspergillus spp.</i>
Tolnaftate	Inhibits ergosterol biosynthesis similar to allylamines	Topical	Dermatophytes
Pentamidine	Inhibits DNA synthesis	Systemic	Prevent or treat <i>Pneumocystis jiroveci</i> in HIV/AIDS patients



KEY CONCEPTS

- Superficial mycoses are limited to the outermost layers of the skin (stratum corneum) with little tissue damage and generally no inflammatory response.
- Medically important superficial mycoses are pityriasis versicolor, tinea nigra, black piedra, and white piedra.

A 30-year-old man presents to his dermatologist with multiple hypopigmented lesions on his chest and back. On examination, the lesions have a dry, scaly appearance. A direct microscopic examination of a KOH preparation revealed the presence of yeast cells and hyphae that resembled spaghetti and meatballs.



Multiple small- to medium-sized hypopigmented macules (Reproduced, with permission, from Wolff K, Johnson RC, Saavedra A. *Fitzpatrick's Color Atlas and Synopsis of Clinical Dermatology*. 7th ed. New

Pityriasis Versicolor

Etiology and Epidemiology	Pityriasis versicolor is caused by <i>Malassezia furfur</i> ; (also <i>M. globosa</i> and <i>M. sympodialis</i>), a lipophilic yeast. <i>M. furfur</i> is part of the normal flora and is transmitted by direct contact. Pityriasis versicolor is a common infection with worldwide distribution and a higher prevalence in the tropics, in patients who have undergone renal transplant, and in patients with AIDS.
Clinical Manifestations	Pityriasis versicolor is characterized by dry, scaly, hyperpigmented, or hypopigmented lesions on the trunk, abdomen, and arms. <i>M. furfur</i> can cause systemic disease in patients receiving intravenous lipid infusion therapy and seborrheic dermatitis in patients with AIDS.
Pathogenesis	Pityriasis versicolor is not associated with a host immune response, and no virulence factors are known.
Laboratory Diagnosis	Direct microscopic examination of scaly lesions in a KOH preparation reveals a characteristic “spaghetti and meatballs” appearance of yeast and hyphae. It can be cultured on growth medium supplemented with fatty acids (layer of olive oil).
Treatment and Prevention	Pityriasis versicolor is treated topically with selenium sulfide, miconazole, or ketoconazole. Good hygiene is important in prevention.
Notes	

A 12-year-old boy presents to the family’s physician with brownish-black, nonscaly macular lesions on his palms and soles. Microscopic examination of skin scrapings after KOH treatment revealed brownish pigmented yeast cells and septate hyphae.



Uniformly tan macule on the plantar foot (Reproduced, with permission, from Wolff K, Johnson RC, Saavedra A. *Fitzpatrick's Color Atlas and Synopsis of Clinical Dermatology*. 7th ed. New York, NY: McGraw-Hill; 2013.)

Tinea Nigra

Etiology and Epidemiology	Tinea nigra is caused by <i>Exophiala werneckii</i> , a melanin-producing, dimorphic fungus. <i>E werneckii</i> is found in the soil and often transmitted by injury. Tinea nigra is endemic in the tropics.
Clinical Manifestations	Tinea nigra is characterized by a flat brown to black, nonscaly macular lesions of the palms of the hands and soles of the feet with other areas less often affected.
Pathogenesis	<i>E werneckii</i> does not elicit a host immune response, and no virulence factors are known.
Laboratory Diagnosis	Direct microscopic examination of skin scrapings in a KOH preparation reveals brown pigmented yeast cells and hyphae. Black colonies of <i>E werneckii</i> are observed on culture.
Treatment and Prevention	Tinea nigra is treated topically with salicylic acid or a topical antifungal agent (such as ketoconazole or terbinafine). Good hygiene is an important preventive measure.

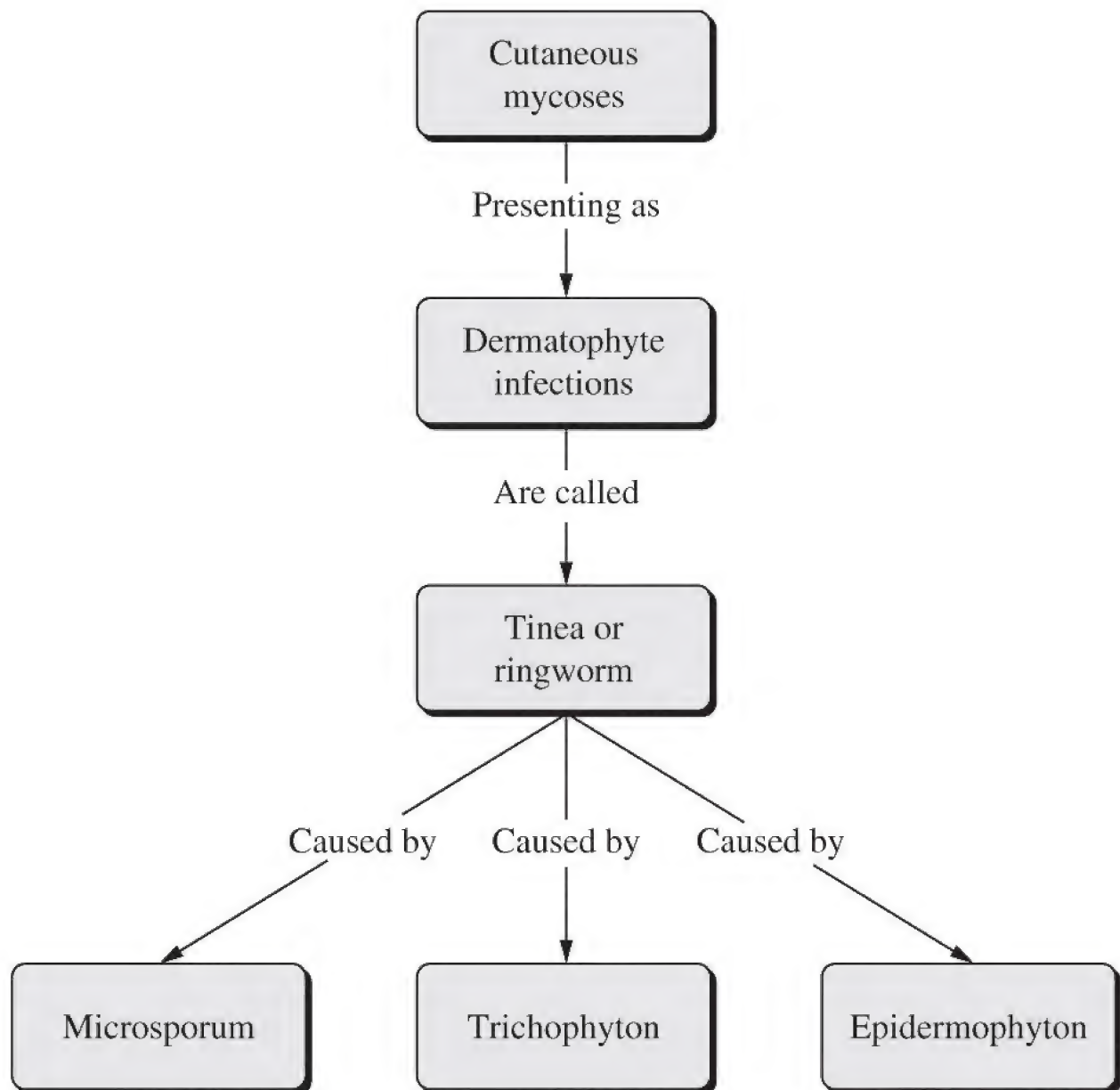
Notes

A 50-year-old man living in a homeless shelter is seen at a local clinic with

cream-colored, soft nodules on the hair shafts of his moustache. Microscopic examination of hairs in a KOH preparation reveals that the white nodules on the hair shaft are comprised of septate hyphae.

White Piedra

Etiology and Epidemiology	White piedra is an infection of the scalp, moustache, facial beard, axillary hair, or pubic hair caused by <i>Trichosporon</i> species such as <i>T. asahii</i> (formerly <i>T. beigeli</i>). Black piedra is an infection of the scalp hair caused by <i>Piedraia hortae</i> . Infected hairs on shared combs or hairbrushes transmit white and black piedra. Both white and black piedra are more common in young adults in tropical areas.
Clinical Manifestations	White piedra is characterized by cream-colored soft nodules on the hair shaft. Black piedra is characterized by hard, brown to black nodules attached to the hair shaft. <i>T. asahii</i> can cause disseminated trichosporonosis, mainly in neutropenic and immunocompromised patients.
Pathogenesis	<i>T. asahii</i> and <i>P. hortae</i> do not elicit a host immune response, and no virulence factors are known.
Laboratory Diagnosis	Direct microscopic examination of hairs in a KOH preparation reveals white to light brown nodules with septate hyphae on the hair shaft (white piedra) or dark pigmented nodules containing dark septate hyphae on the hair shaft (black piedra).
Treatment and Prevention	Piedra is treated by removal of the infected hair and application of a topical antifungal azole agent combined with good personal hygiene.
Notes	



KEY CONCEPTS

- Cutaneous mycoses are limited to the keratinized tissues of the skin, hair, or nails without penetration of deeper tissues. A host inflammatory response is elicited.
- Medically important cutaneous mycoses are the dermatophyte infections, classically called tinea or ringworm.
- Dermatophytes belong to three genera: *Microsporum*, *Trichophyton*, and *Epidermophyton*.
- Dermatophytes are grouped by their natural habitat or reservoir as either **anthropophilic** (human skin pathogens), **zoophilic** (animal skin pathogens), or **geophilic** (soil associated).
- Tinea infections are categorized clinically by the affected anatomic site (eg, tinea capitis, scalp; tinea pedis, feet (athlete's foot); tinea corporis, body; tinea barbae, beard; tinea cruris, groin (jock itch); tinea unguium, nails; tinea manuum, hands).

An 11-year old boy is seen by a pediatrician with patchy alopecia of the scalp. On examination, he has circular, erythematous, dry, scaly lesions on the scalp with areas of alopecia. His pet dog has similar lesions. Examination of the scalp with a UV light revealed hair that fluoresces. A microscopic examination of a KOH preparation of scrapings of the scalp lesions revealed the presence of hyphae.

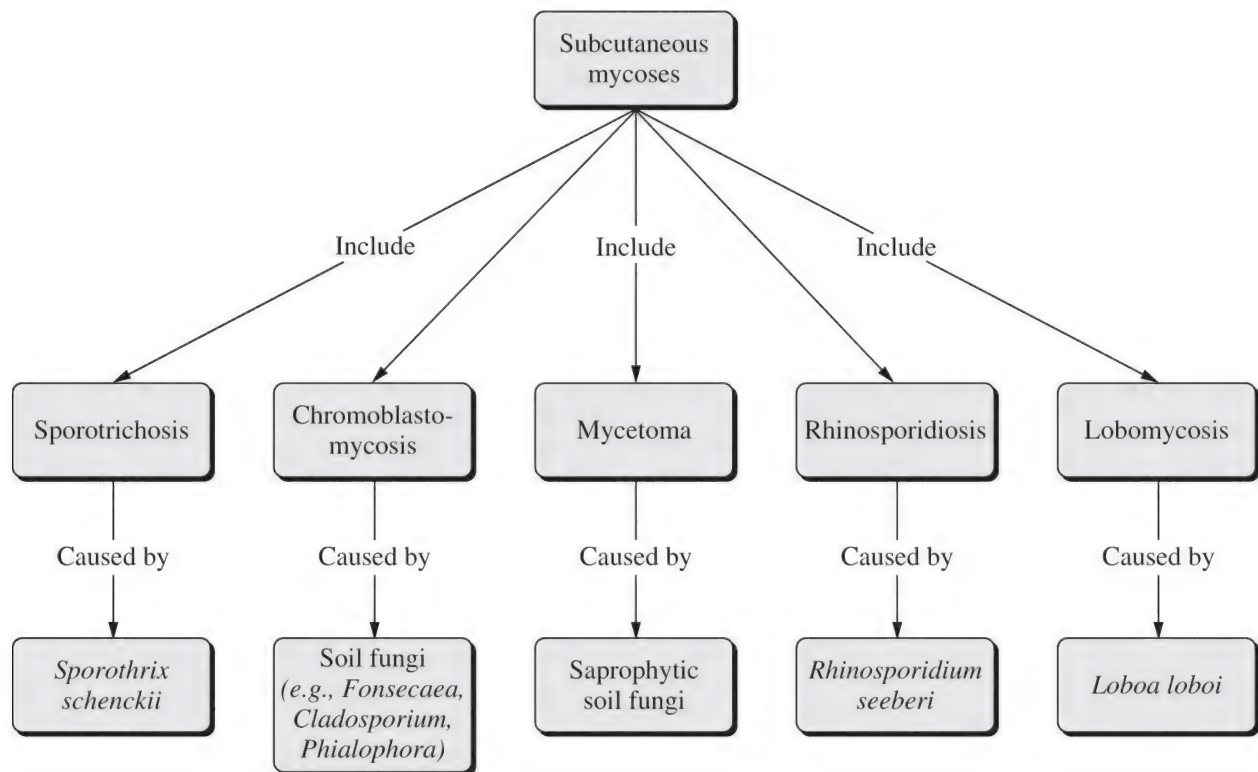


Image depicts scalp region of head with cutaneous lesions.

(Source: Centers for Disease Control and Prevention, Atlanta, GA.)

Tinea Capitis (Ringworm)

Etiology and Epidemiology	Tinea capitis or scalp ringworm is caused predominately by <i>Trichophyton tonsurans</i> and the zoophilic <i>Microsporum canis</i> . Tinea infections are transmitted directly by close contact with infected humans or animals (zoophilic species) or indirectly by contact with detached skin or hair in items such as clothing, towels, combs, and brushes. Tinea capitis is predominately a disease of children and can spread rapidly in a family or school. Onychomycosis (dermatophyte infection of the nails) affects 20% of the adult U.S. population with significant social morbidity.
Clinical Manifestations	Tinea capitis is characterized by dry, ring-like, scaly, itchy, erythematous lesions on the scalp and may present as areas of alopecia.
Pathogenesis	Dermatophytes are keratinophilic with infection localized to the skin, hair, and nails. Dermatophytes secrete keratinase that digests keratin and evoke an inflammatory response that limits infection. Deeper tissue invasion is rare because of nonspecific host defense mechanisms. Patients with defects in cell-mediated immunity are at risk of chronic or disseminated dermatophyte infections.
Laboratory Diagnosis	Direct microscopic examination of skin, hair, or nails in a KOH preparation demonstrates hyphae and conidia characteristic of the dermatophyte. Certain fungi (eg, <i>Microsporum</i>) fluoresce under UV light.
Treatment and Prevention	Dermatophyte infections are treated systemically with griseofulvin or terbinafine. Adjunctive therapy includes use of a shampoo with antifungal properties. Onychomycosis is treated systemically with itraconazole or terbinafine. Good personal hygiene is important in prevention.
Notes	Tinea cruris (“jock itch”): <i>T rubrum</i> , <i>T mentagrophytes</i> , or <i>Epidermophyton floccosum</i> ; Tinea pedis (“athlete’s foot”): <i>T rubrum</i> , <i>T mentagrophytes</i> , or <i>E floccosum</i> ; Tinea barbae : zoophilic <i>T verrucosum</i> , <i>T mentagrophytis</i> , or <i>T rubrum</i> ; Tinea unguium (onychomycosis): <i>T rubrum</i> , <i>T mentagrophytes</i> , or <i>E floccosum</i> .



KEY CONCEPTS

- Subcutaneous mycoses are limited to the deeper skin structures often associated with traumatic inoculation of subcutaneous tissue.
- The source of the causative agent is the soil or vegetation.
- Human-to-human transmission does not occur with subcutaneous mycoses.
- Subcutaneous mycoses are characterized by a chronic and indolent clinical course.

- Medically important subcutaneous mycoses are sporotrichosis, chromoblastomycosis, mycetoma, rhinosporidiosis, and lobomycosis.

A 60-year-old woman is seen by her internist with a complaint of an open sore on her thumb that has not healed. On physical examination, she has an ulcerative lesion on the thumb and several nodular lesions on the arm along the lymphatic chain. She is a master gardener and reports being pricked by a rose thorn 2 weeks earlier.

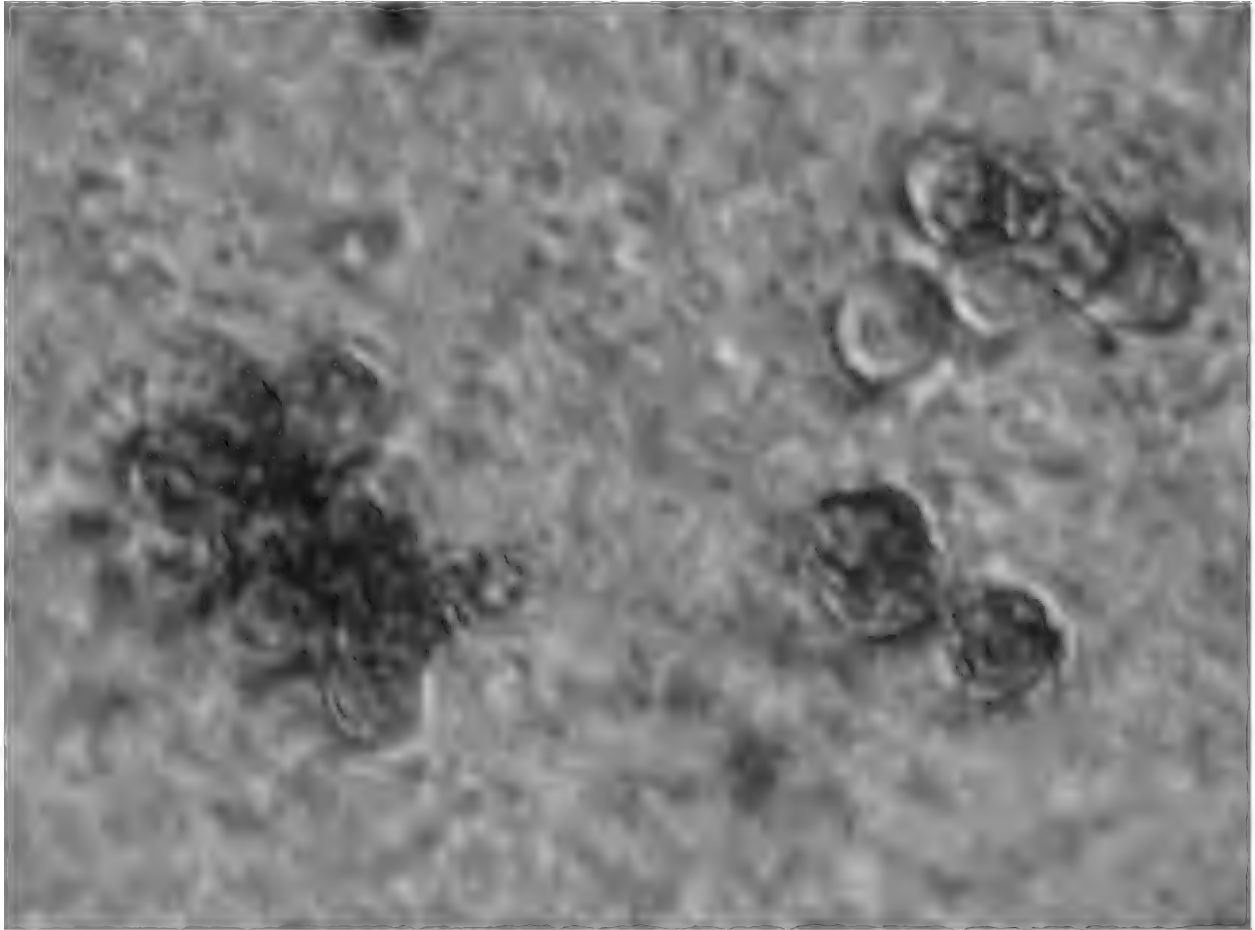


Ulcerated nodule seen on the thumb with proximal lymphatic spread represented by subcutaneous nodules. (Reproduced, with permission, from Goldsmith LA, Katz SI, Gilchrest BA, Paller AS, Leffell DJ, Wolff K, eds. *Fitzpatrick's Dermatology in General Medicine*. 8th ed. New York: McGraw-Hill; 2012. Used with permission from Takeji Nishikawa, MD.)

Sporotrichosis

Etiology and Epidemiology	Sporotrichosis is caused by the dimorphic fungus <i>Sporothrix schenckii</i> . Sporotrichosis is transmitted from the soil or decaying vegetation by occupational or recreational exposure to the conidia or hyphal fragments via a puncture wound (eg, thorn prick). Sporotrichosis is frequently seen in gardeners. Rose thorns, sphagnum moss, and baled hay are sources of infection.
Clinical Manifestations	Sporotrichosis is characterized by ulcers at the site of inoculation and nodules along the draining lymphatic chain.
Pathogenesis	Sporotrichosis is a localized infection that induces an inflammatory response. Production of melanin by <i>S schenckii</i> may inhibit killing by neutrophils. Cell-mediated immunity is the major host defense mechanism.
Laboratory Diagnosis	Diagnosis is made by culture demonstration of dimorphism (a mold at 25°C and yeast at 37°C). Microscopic examination of histopathologic specimens stained with either Gomori methenamine silver stain or periodic acid-Schiff stain can also be used.
Treatment and Prevention	Sporotrichosis is treated systemically with itraconazole. For severe or life-threatening disease, amphotericin B can be used initially. Preventive measures include wearing gloves and protective clothing when handling rose bushes, sphagnum moss, hay bales, and wood splinters.
Notes	

A 40-year-old male native Brazilian Indian presents to a medical clinic with warty lesions on his legs that have spread slowly over the past year. He works as a laborer in the Amazon rainforest. On examination, the lesions appear as crusted, verrucous, wart-like nodules on the leg. Direct microscopic examination of skin scrapings revealed copper-colored, round, sclerotic bodies.



Brownish, sclerotic cells in cutaneous biopsy (Reproduced, with permission, from Carroll KC, Butel JS, Morse SA, eds. Jawetz, Melnick & *Adelbergs Medical Microbiology*. 27th ed. New York: McGraw-Hill; 2016.)

Chromoblastomycosis

Etiology and Epidemiology	Chromoblastomycosis is a subcutaneous fungal infection caused by one of several dematiaceous (pigmented) fungi that reside in soil or on vegetation (<i>Fonsecaea pedrosi</i> , <i>F compacta</i> , <i>Phialophora verrucosa</i> , <i>Rhinocladiella aquaspersa</i> , <i>Cladophialophora</i> [<i>Cladosporium</i>] <i>carrii</i>). The organism is typically introduced by a traumatic inoculation into tissue. It is endemic in the tropics, and rarely seen in the United States. Most infections are chronic and occur on the feet and legs of barefoot workers.
Clinical Manifestations	Chromoblastomycosis is characterized by the slow development of wart-like lesions that progress to a cauliflower appearance at the inoculation site.
Pathogenesis	Chromoblastomycosis lesions exhibit an inflammatory response with keratinolytic microabscesses and epithelial cell hyperplasia.
Laboratory Diagnosis	Skin scrapings in a KOH preparation reveal dark, copper-colored spherical cells (sclerotic bodies) that are pathognomonic for chromoblastomycosis regardless of the etiologic agent. Specimens should be cultured on Sabouraud dextrose agar (SDA) containing antibiotics to identify the agent.
Treatment and Prevention	Chromoblastomycosis is treated by surgical excision with wide margins, and/or with itraconazole. Wearing shoes is a preventive measure.
Notes	

A 33-year-old male Sudanese immigrant presents to a medical clinic with painful abscesses on his left foot. He was a field worker in Sudan and recalled multiple splinter injuries to his feet. On examination, the foot is indurated with ulcerative lesions and a purulent fluid discharge from draining sinuses. Sclerotia were detected in fluid exudates.



Patient foot with ulcerative lesions (Source: Centers for Disease Control and Prevention, Atlanta, GA.)

Mycetoma

Etiology and Epidemiology	Mycetoma (also called Madura foot) is a chronic infection of subcutaneous tissue by a variety of saprophytic fungi in the soil. The agents of mycetoma are ubiquitous and transmitted by traumatic inoculation most commonly in individuals who go barefoot. Mycetoma is common in the tropics but uncommon in the United States. It may also be caused by actinomycetes (actinomycetoma).
Clinical Manifestations	Mycetoma is characterized by localized abscess formation, edema, induration, and inter-connecting draining sinuses often of the foot after a traumatic injury. The granulomas can extend to muscle and bone and result in deformities.
Pathogenesis	The granulomatous lesions of mycetoma contain sclerotia (granules, grains) that consist of a compact mass of hyphae.
Laboratory Diagnosis	Diagnosis is made by macroscopic identification of granules from sclerotia. The granules can be dissected out from the pus of biopsy for culture. The size, shape, and color of the granules help to identify the etiologic agent.
Treatment and Prevention	Surgical debridement combined with extended treatment with antifungal drugs depending on the etiologic agent. Wearing shoes is a preventive measure.
Notes	

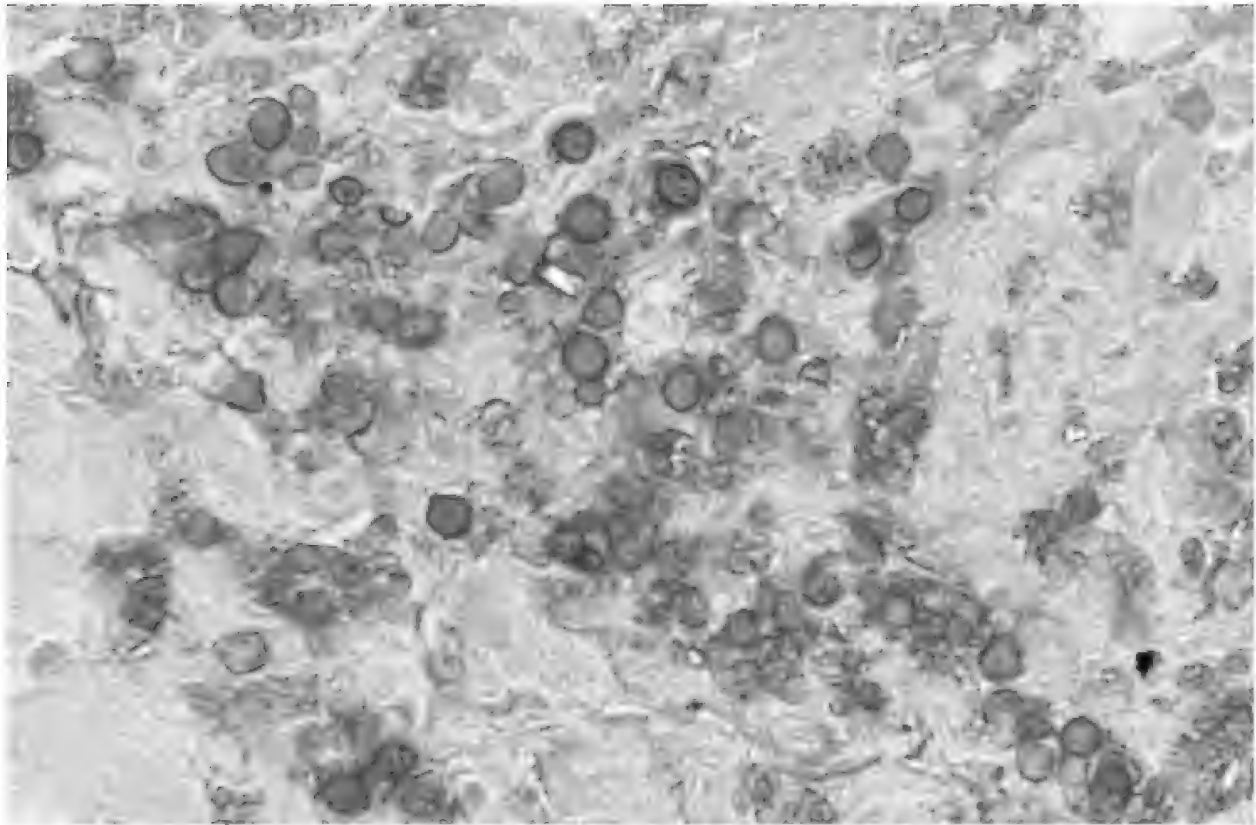
A 30-year-old fisherman from Sri Lanka is seen in a “Doctors Without Borders” clinic with a large mass in his nose. On examination, the patient has a large, nontender nasal polyp and a seropurulent nasal discharge. Microscopic examination of the discharge revealed neutrophils and spherules filled with endospores.

Rhinosporidiosis

Etiology and Epidemiology	Rhinosporidiosis is caused by <i>Rhinosporidium seeberi</i> and is associated with divers and traumatic inoculation. Fish are the natural reservoir for <i>R seeberi</i> . Most cases are reported from India and Sri Lanka.
Clinical Manifestations	Rhinosporidiosis is characterized by the development of painless, pedunculated nasal polyps.
Pathogenesis	Lesions of rhinosporidiosis are characterized by an inflammatory cell infiltrate with abscess formation and tissue necrosis.
Laboratory Diagnosis	Direct microscopic examination of excised tissue or nasal discharge in a KOH preparation reveals large spherules containing endospores.
Treatment and Prevention	Treatment of rhinosporidiosis is surgical removal or local injections of amphotericin B.
Notes	

A 25-year-old geologist from New York presented to a dermatologist with a

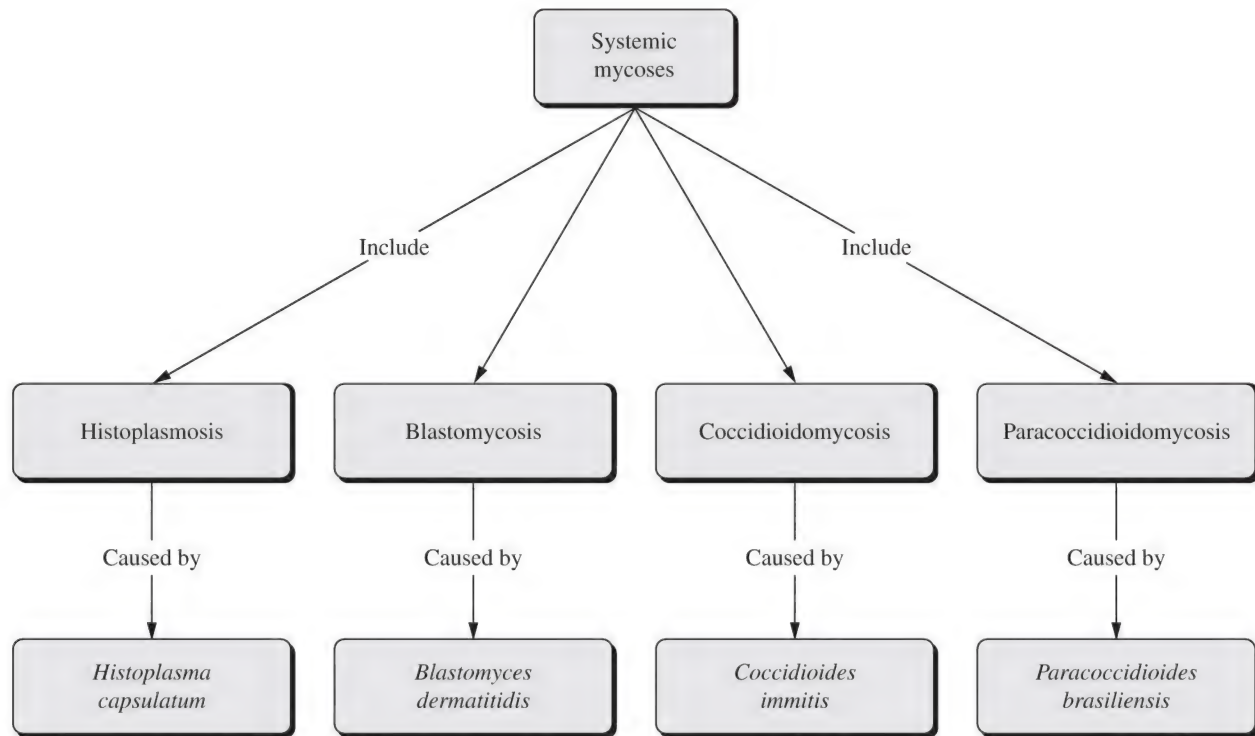
slowly-growing, painless, keloidal nodule on her right upper arm. She noticed a small nodule on her arm about 2 years earlier when she was working as a Peace Corps volunteer in the jungles of Venezuela. Physical examination was unremarkable other than the reddish, plaque-like lesion on her arm. Examination of tissue sections of the biopsied lesion stained with Gomori methenamine silver showed the presence of chains of spheroidal yeast cells.



Yeast cells in biopsy of lesion (Source: Centers for Disease Control and Prevention, Atlanta, GA.)

Lobomycosis

Etiology and Epidemiology	Lobomycosis is caused by <i>Loboa loboi</i> and often associated with a traumatic inoculation of the agent. <i>L. loboi</i> causes natural infections of dolphins.
Clinical Manifestations	Lobomycosis is characterized by hard, painless nodules (keloids) on the upper extremities, face, and ear.
Pathogenesis	Lobomycosis lesions resemble the lesions of chromoblastomycosis and mycetoma.
Laboratory Diagnosis	Direct microscopic examination of excised tissue in a KOH preparation reveals yeast cells in long chains.
Treatment and Prevention	Surgical excision is curative for lobomycosis.
Notes	



KEY CONCEPTS

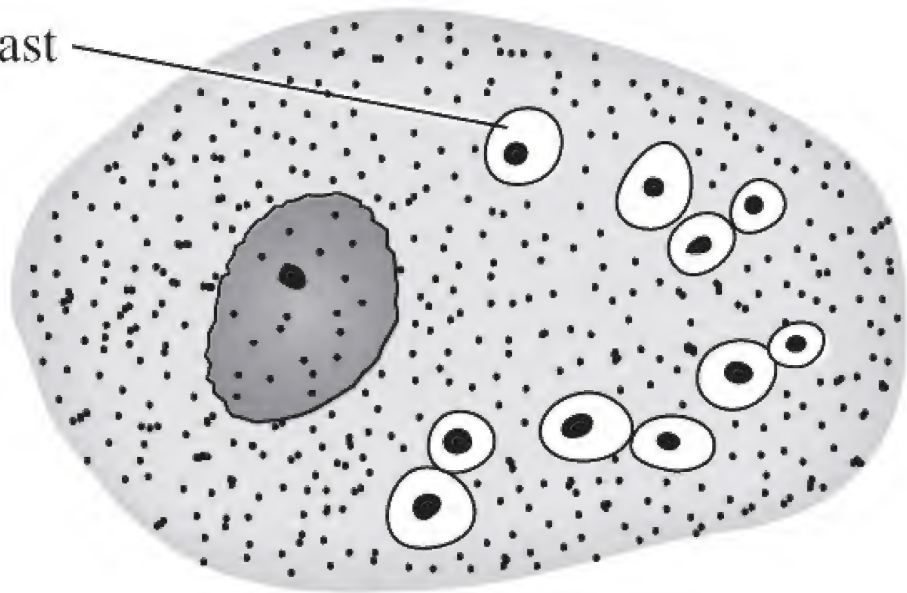
- Fungi that cause systemic infections are inherently virulent and capable of causing disease in otherwise healthy individuals.
- Systemic fungal pathogens cause endemic disease in defined geographic areas.
- Systemic fungal pathogens are **thermally dimorphic**, growing as the mycelial form in the soil and the yeast form at body temperature.
- Systemic fungal pathogens are transmitted by the inhalation of spores that

germinate in the lungs. There is no human-to-human transmission.

- Medically important systemic mycoses are **histoplasmosis**, **blastomycosis**, **coccidioidomycosis**, and **paracoccidioidomycosis**.

A 35-year-old real estate agent from Kentucky was seen by an internist with complaints of fever, chest pain, shortness of breath, and a nonproductive cough. The patient renovates old homes for resale. Two weeks before onset of the current symptoms, he worked on a house that was contaminated with bird droppings. On physical examination, his oral temperature was 37.5°C, and chest auscultation revealed crackles in both lungs. A chest X-ray and urine antigen test were ordered.

Intracellular yeast

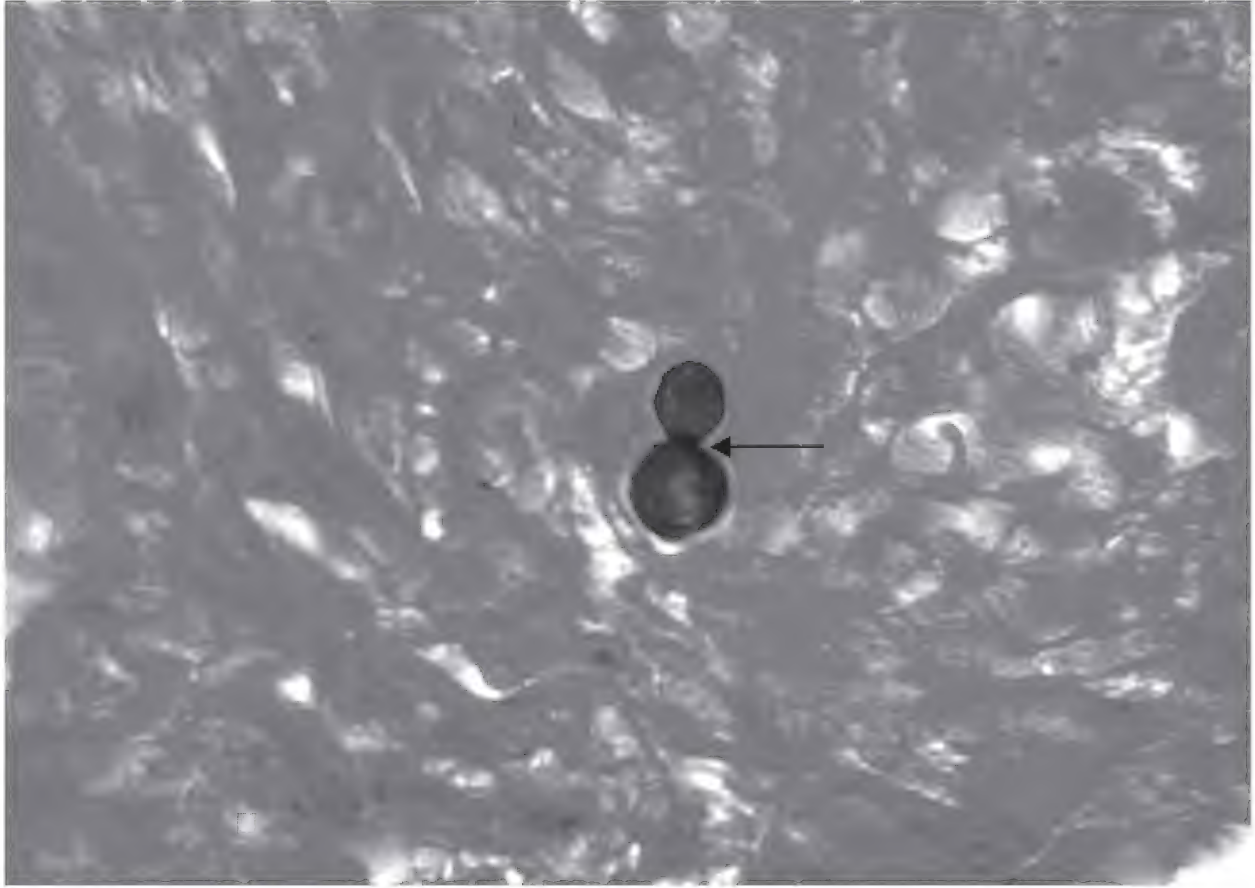


Yeast within macrophage, is a common feature of this disease infection. (Reproduced with permission from Brooks GF et al. *Medical Microbiology*. 19th ed. Originally published by Appleton & Lange. Copyright © 1991 by McGraw-Hill.)

Histoplasmosis

Etiology and Epidemiology	Histoplasmosis is caused by <i>Histoplasma capsulatum</i> , transmitted by inhalation of aerosolized spores (microconidia) after disturbance of contaminated soil or bird droppings. Histoplasmosis occurs worldwide but most cases occur in the United States where it is endemic in the Ohio and Mississippi River valleys . <i>H capsulatum</i> grows in soil, particularly in soil containing bird (especially starlings) and bat droppings.
Clinical Manifestations	Most infections (>90%) are asymptomatic, self-limited, and involve immunocompetent individuals. Chronic pulmonary and progressive histoplasmosis occur in 1% of cases, usually in immunocompromised persons or because of exposure to a large inoculum of the organism. Disseminated histoplasmosis is rare but may develop in immunocompromised patients with T-cell defects (eg, in patients with HIV/AIDS) and solid-organ transplant recipients. Disseminated histoplasmosis has a mortality rate of about 10% in patients with HIV or AIDS.
Pathogenesis	Inhaled microconidia of <i>H capsulatum</i> multiply intracellularly as yeast forms in macrophages and continue to grow until an immune response is elicited, resulting in a localized granuloma. Disseminated histoplasmosis involves invasion of cells of the reticuloendothelial system. <i>H capsulatum</i> survives phagolysosomal killing by inducing a rise in lysosomal pH, thereby inactivating degradative enzymes.
Laboratory Diagnosis	Direct microscopic examination of clinical specimens (sputum, tissue) stained with Giemsa or Wright's stain reveals yeast within macrophages. An <i>H capsulatum</i> -specific polysaccharide antigen can be detected by enzyme-linked immunoassay in blood and urine of patients with disseminated disease.
Treatment and Prevention	Treatment is often not required for acute pulmonary infections, which are usually self-limited. For mild to moderate disease, an azole (itraconazole or fluconazole) can be used. For moderately severe to severe disease, amphotericin B is recommended as initial therapy. Avoidance of exposure in high endemic areas is a preventive measure.

A 55-year-old man from rural Arkansas presents to his primary care physician with complaints of chest pain and fever. He is a former smoker and works as a guide for a local hunt club. Chest X-ray reveals a right lower lobe pulmonary mass suggestive of lung cancer. Cytologic examination of the lung tissue shows broad-based budding yeast.

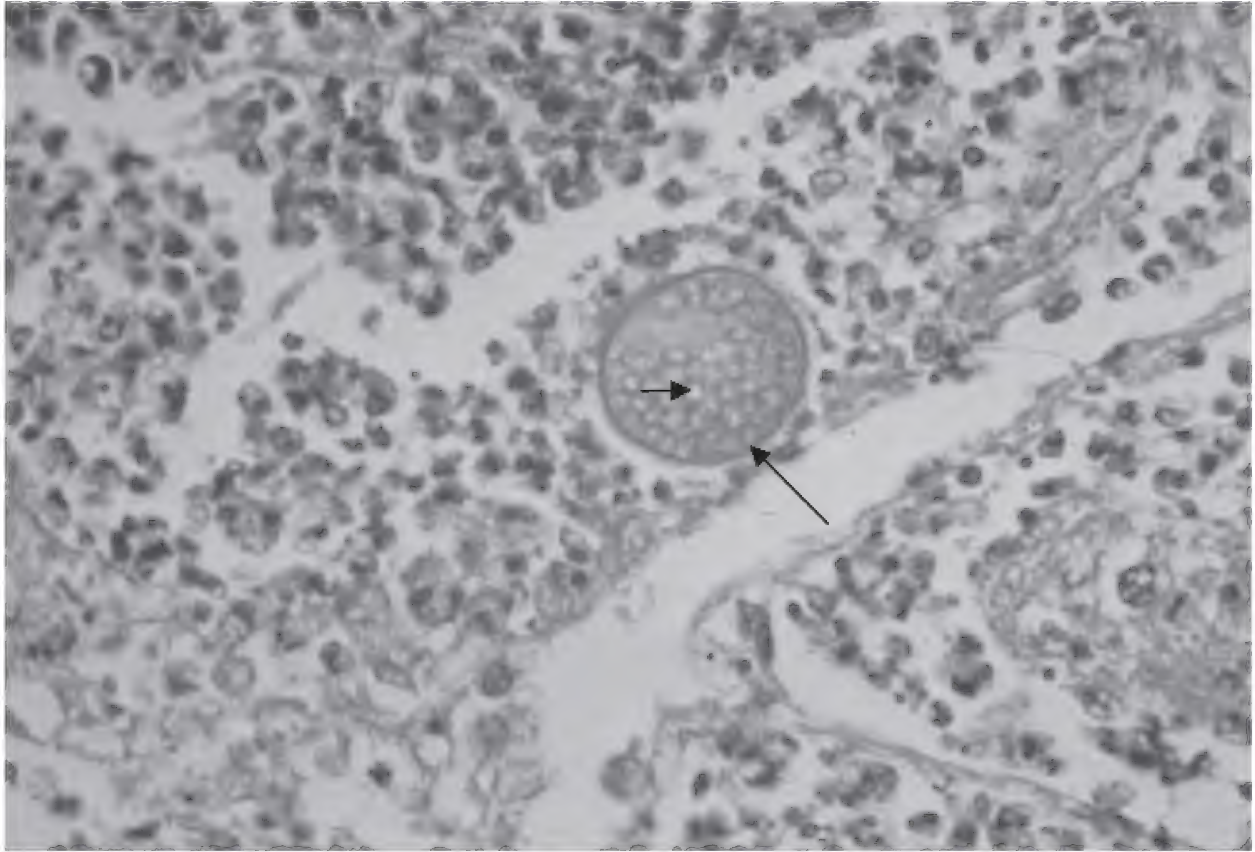


Broad-based budding yeast (8–15 μm). Arrow points to broad base of the budding yeast. (Source: Centers for Disease Control and Prevention, Atlanta, GA.)

Blastomycosis (North American Blastomycosis)

Etiology and Epidemiology	Blastomycosis is caused by <i>Blastomyces dermatitidis</i> and is transmitted by the inhalation of aerosolized spores (conidia) after disturbance of contaminated soil. Blastomycosis is endemic in the Ohio and Mississippi River valley regions as well as in the Missouri and Arkansas River basins of the United States. Soil enriched with organic matter is the reservoir of infection. The typical patient has extensive outdoor occupational or recreational exposure.
Clinical Manifestations	Symptomatic infection is common (50% of cases) with pulmonary symptoms of chest pain, sputum production, and fever. Clinical features are similar to histoplasmosis and may mimic tuberculosis or lung cancer. Progressive disseminated blastomycosis may involve secondary sites, most commonly the skin (70%), bone (33%), genitourinary tract (25%), and central nervous system (10%).
Pathogenesis	After inhalation of <i>Blastomyces</i> conidia, a mixed inflammatory response occurs with infiltration of neutrophils and macrophages with subsequent granuloma formation. Cell-mediated immunity is an important determinant in recovery from infection.
Laboratory Diagnosis	Direct microscopic examination of sputum, pus, exudates, or tissues in a KOH preparation reveals the characteristic broad-based budding yeast cells of <i>B dermatitidis</i> . After isolation by culture on Sabouraud's at 30°C, identification is confirmed by conversion to the yeast form after cultivation on a rich medium at 37°C.
Treatment and Prevention	Itraconazole is usually used to treat non-life-threatening disease. Amphotericin B is used for life-threatening, disseminated blastomycosis. Avoidance of exposure in highly endemic areas is a means of prevention.
Notes	

A 45-year-old man is seen in the Emergency Department reporting fatigue, fever, myalgias, chest pain, and shortness of breath that have lasted a week. He recently returned from a trip to Arizona where he spent most of his time outdoors camping and hiking. On physical examination, he had a fever of 38.5°C, a deep cough, and tender joints. Laboratory workup revealed peripheral eosinophilia. Microscopic examination of a sputum specimen reveals spherules.

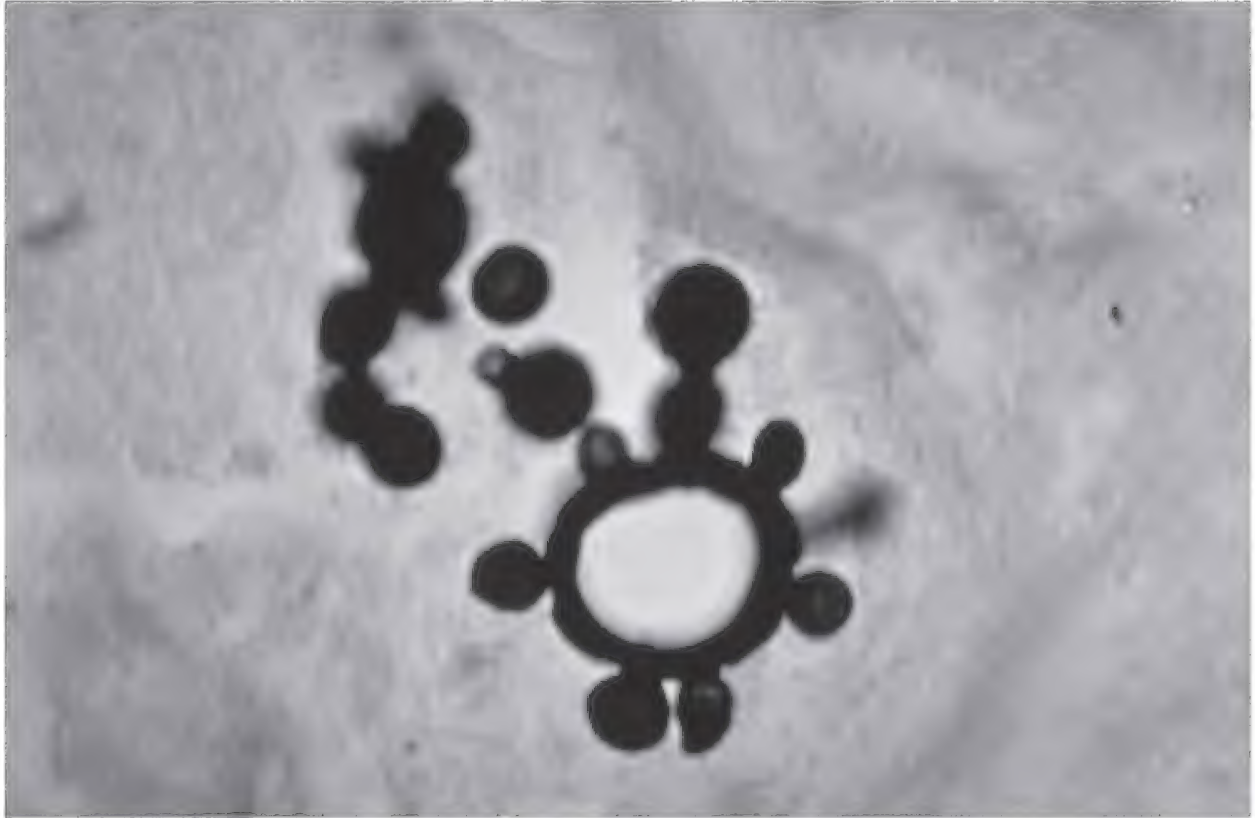


Long arrow points to a spherule in tissue section. Spherules are thick-walled structures containing many endospores. Short arrow points to an endospore. (Source: Centers for Disease Control and Prevention, Atlanta, GA.)

Coccidioidomycosis

Etiology and Epidemiology	Coccidioidomycosis is caused by <i>Coccidioides immitis</i> or <i>C posadasii</i> and is transmitted by inhalation of aerosolized arthroconidia after contaminated soil is disturbed by humans (excavation) or nature (dust storms, earthquakes). Coccidioidomycosis is endemic in arid regions of the southwestern United States, parts of Mexico, and South America . Disseminated disease occurs most frequently in immunocompromised hosts..
Clinical Manifestations	Infections are largely asymptomatic, but about 40% develop pulmonary disease that can be self-limited. Disseminated extrapulmonary coccidioidomycosis occurs in about 5% of cases and can involve skin, bone, and CNS with meningitis. Untreated disseminated disease has a mortality of about 50%.
Pathogenesis	Inhaled arthroconidia germinate in the lungs to form spherules filled with endospores. Organisms are phagocytized by macrophages and neutrophils. Fungal proteases and components of the spherule outer wall contribute to virulence. Cell-mediated immunity is a key determinant to disease resolution.
Laboratory Diagnosis	Direct examination of clinical specimens (sputum, tissue) in a KOH preparation reveals characteristic spherules . IgM antibodies to coccidioidin can be detected with a latex agglutination test. Eosinophilia has been noted as a useful laboratory marker of coccidioidomycosis. <i>C immitis</i> and <i>C posadasii</i> cultures are a biohazard in the clinical laboratory and should be handled accordingly.
Treatment and Prevention	Symptomatic primary infection can be self-limited and may require only supportive treatment, although fluconazole, or itraconazole, may reduce the symptoms. Systemic amphotericin B followed by several months of oral therapy with fluconazole or itraconazole is used to treat severe disease. Coccidioidal meningitis is generally treated with oral fluconazole since it achieves CSF penetration. In cases of severe disease, amphotericin B is sometimes initially used in combination with fluconazole. Avoidance of travel to endemic areas and activities that generate dust exposure in endemic areas are preventive measures.

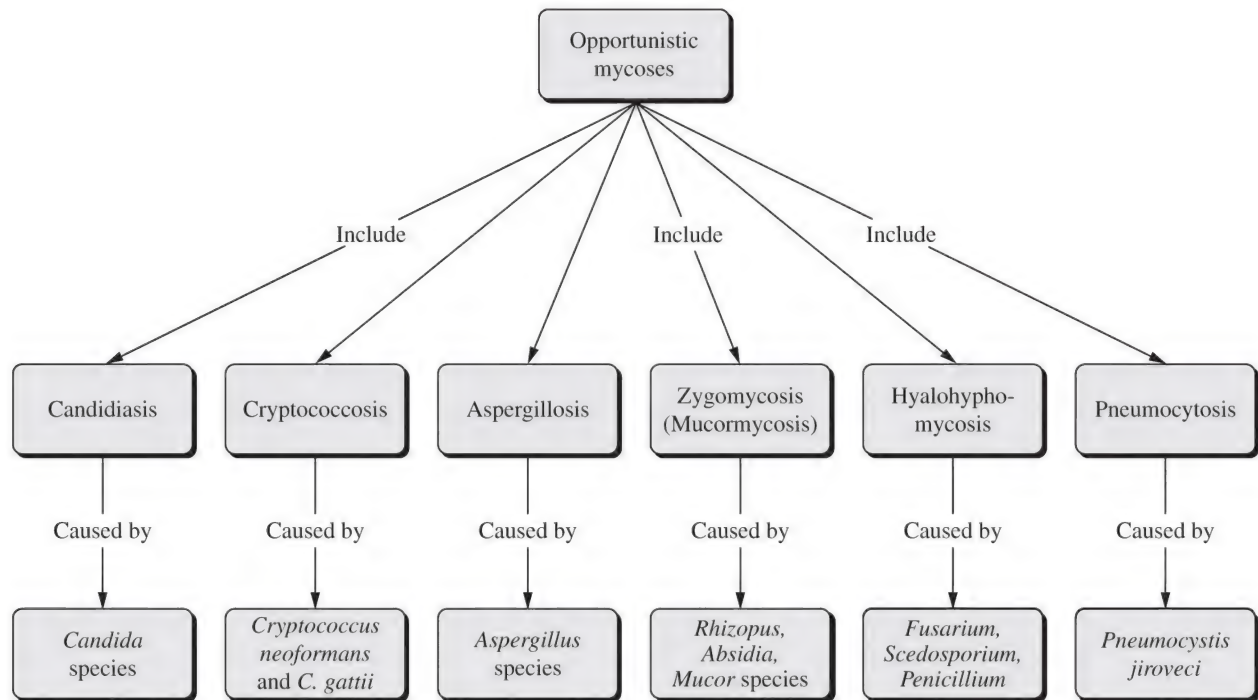
A 50-year-old male laborer from Brazil is seen in a medical clinic run by Doctors Worldwide with history of a chronic cough, fever, malaise, and weight loss. He presents to the clinic with painful, ulcerative lesions in the nasal and oral cavities. Direct examination of scrapings from the ulcerative lesions in a KOH preparation revealed yeast with multiple buds in a “pilot wheel” configuration.



Yeast cells (15–30 μm) with multiple buds resembling a “pilot wheel.” (Source: Centers for Disease Control and Prevention, Atlanta, GA.)

Paracoccidioidomycosis (South American Blastomycosis)

Etiology and Epidemiology	Paracoccidioidomycosis is caused by <i>Paracoccidioides brasiliensis</i> and transmitted by the inhalation of aerosolized conidia after contaminated soil is disturbed. Paracoccidioidomycosis is restricted to endemic regions of Central and South America . Symptomatic and progressive paracoccidioidomycosis is nine times more common in males than females because of an estrogen-mediated inhibition of mycelial-to-yeast conversion <i>in vivo</i> . It is not communicable.
Clinical Manifestations	Asymptomatic infections are common. Symptomatic infections present as primary and chronic pneumonia characterized by fever, cough, sputum production, and chest pain, symptoms similar to those of histoplasmosis and blastomycosis. Disseminated extrapulmonary disease is rare but usually presents as oral, nasal, and facial papular or verrucous ulcerative lesions and lymphadenopathy.
Pathogenesis	Inhaled conidia germinate in the lung to the pathogenic yeast form. A fungal, estrogen-binding protein inhibits the mold-to-yeast phase conversion in the presence of estrogen, accounting for the clinical disease predilection in males. Cell-mediated immunity is a primary determinant of recovery from infection.
Laboratory Diagnosis	Direct microscopic examination of clinical specimens (sputum, bronchoalveolar lavage, tissue) in a KOH preparation reveals characteristic yeast with multiple buds in a "pilot wheel" configuration. Culture to demonstrate thermal dimorphism may be performed for confirmation.
Treatment and Prevention	The azoles (ketoconazole, fluconazole, itraconazole, voriconazole, or posaconazole) are effective, and of these, itraconazole is most commonly used. Severe disease may be treated with amphotericin B. Trimethoprim-sulfamethoxazole is also effective but requires extended treatment to prevent relapse. Avoidance of travel to endemic areas is a means of prevention.
Notes	



KEY CONCEPTS

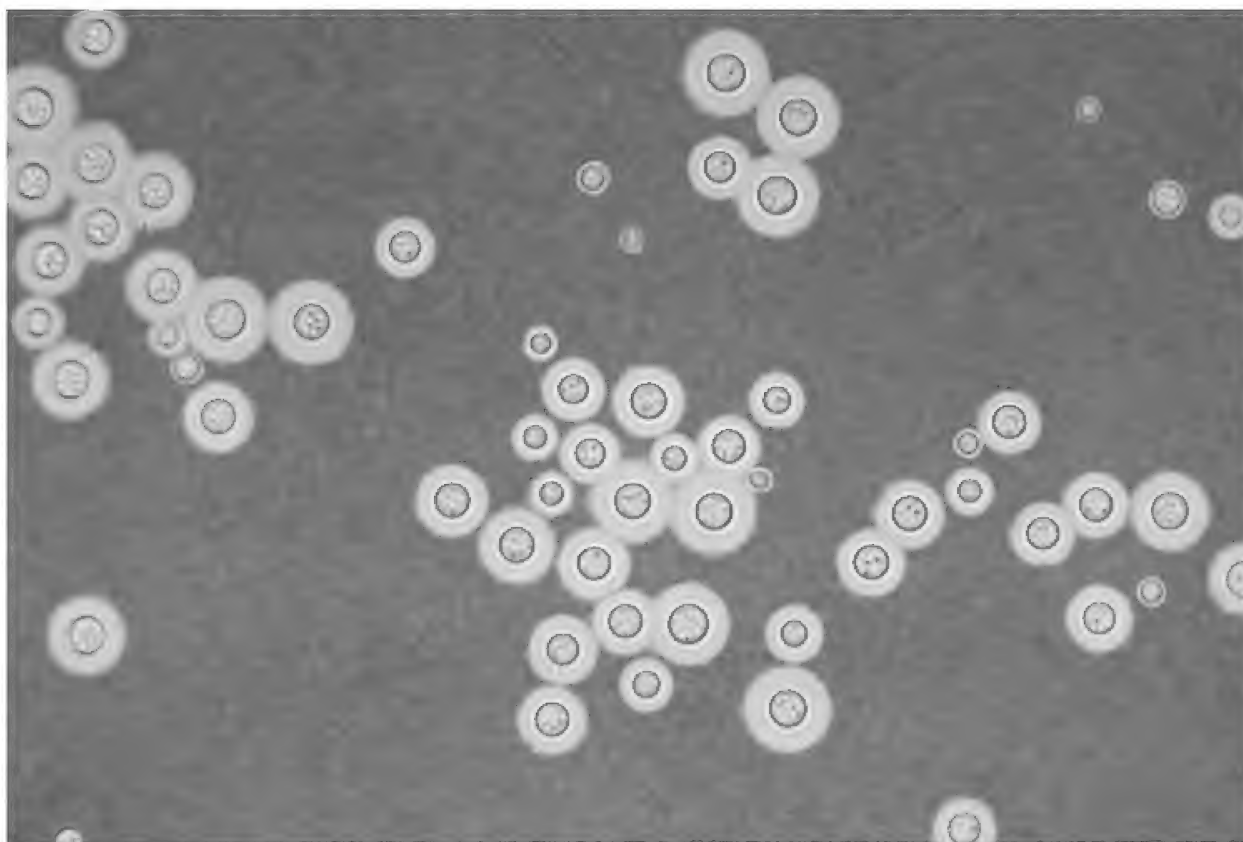
- Opportunistic fungi primarily cause disease in immunocompromised or debilitated individuals.
- Opportunistic fungi cause a diverse spectrum of diseases determined by the immunologic and physiologic state of the individual.
- Medically important opportunistic mycoses are **candidiasis**, **cryptococcosis**, **aspergillosis**, **zygomycosis (mucormycosis)**, **hyalohyphomycosis**, **penicilliosis** and **pneumocytosis**.

A 25-year-old woman presents to her gynecologist with complaints of a recurrent vaginal discharge accompanied by burning and pruritis. Physical examination reveals vaginal erythema and edema. Direct microscopic examination of vaginal secretions in 10% KOH reveals yeast cells.

Candidiasis

Etiology and Epidemiology	Candidiasis is caused by <i>Candida albicans</i> and other <i>Candida</i> species, which are part of the normal flora of the mouth, vagina, and gastrointestinal tract. Risk groups for disseminated disease are debilitated individuals in intensive care units, individuals with diabetes, patients with cancer with chemotherapy-induced neutropenia or mucositis, patients with depressed cell-mediated immunity (HIV/AIDS), and individuals receiving broad-spectrum antibiotics that alter the normal microbial flora.
Clinical Manifestations	Cutaneous candidiasis presents as localized erythema or rash (eg, diaper rash, skin folds of obese individuals) in healthy hosts. Mucocutaneous candidiasis (ie, oral thrush or oropharyngeal candidiasis) presents as creamy, curd-like patches on the oral mucosa and tongue. Vulvovaginal candidiasis appears as a thick, white, vaginal discharge accompanied by burning or itching. Oral thrush and recurrent vulvovaginal candidiasis are common in patients with AIDS. Chronic mucocutaneous candidiasis is a rare but severe infection of skin and mucous membranes that is linked to a specific T-cell defect. Disseminated candidiasis is limited to immunocompromised individuals.
Pathogenesis	Candidiasis occurs when host immune defenses are impaired because of disease or iatrogenic intervention (eg, antibiotics, chemotherapy, corticosteroids). Neutrophils, humoral immunity, and cell-mediated immunity are important defense mechanisms against <i>Candida</i> species.
Laboratory Diagnosis	Direct microscopic examination of clinical specimens demonstrates budding yeast and pseudohyphae . Unlike other <i>Candida</i> species, <i>C. albicans</i> is identified by the formation of germ tubes when incubated in serum at 37°C.
Treatment and Prevention	Oral thrush is often treated with an oral suspension of nystatin. Vulvovaginal and cutaneous infections are commonly treated with topical antifungals (eg, miconazole, clotrimazole). Systemic fluconazole is an alternative, if needed, for oral thrush or vulvovaginal candidiasis. Fluconazole is usually used for treating <i>C. albicans</i> systemic infections. Removal of a source of infection (eg, intravascular catheter) is important. Empiric therapy for systemic invasive candidiasis (while awaiting <i>Candida</i> species identification and susceptibility profile) is usually an echinocandin (micafungin, caspofungin, or anidulafungin) or amphotericin B since some commonly encountered species (eg, <i>C. glabrata</i>) may exhibit resistance or relative resistance to fluconazole.

An 39-year-old HIV-infected woman is seen in the clinic reporting a severe headache and increasing disorientation. Two weeks before this visit, she helped clean out an abandoned house that was inhabited by pigeons. She was admitted to the hospital, where an India ink preparation of cerebrospinal fluid (CSF) obtained by lumbar puncture revealed budding yeast surrounded by a capsule.

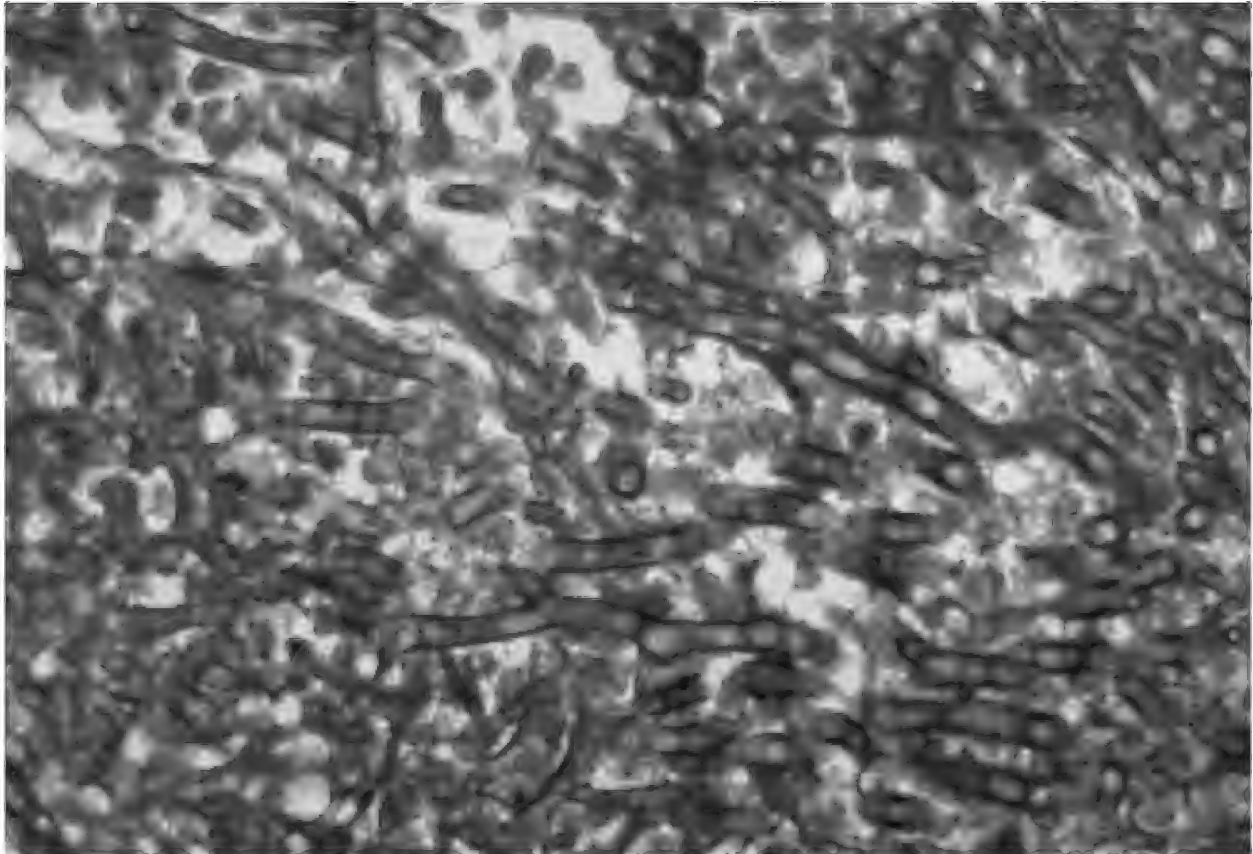


India ink preparation shows budding yeast surrounded by translucent capsule. (Source: Centers for Disease Control and Prevention, Atlanta, GA.)

Cryptococcosis

Etiology and Epidemiology	Primarily caused by <i>Cryptococcus neoformans</i> and transmitted by the inhalation of yeast cells in soil and roosting sites contaminated with pigeon droppings . There is no human-to-human transmission. <i>C. neoformans</i> is not dimorphic, existing only as the yeast form and is the most common cause of meningitis in patients with AIDS. Groups at risk for infection are the immunocompromised, especially patients with HIV and AIDS, and those who have undergone an organ transplant. <i>C. gattii</i> has emerged as a clinically relevant species.
Clinical Manifestations	Cryptococcosis presents with a slow onset of CNS symptoms that progress to chronic meningitis in patients with AIDS. <i>C. neoformans</i> can cause a mild or asymptomatic pneumonia that is usually self-limited. Skin lesions and bone involvement are frequent in disseminated disease.
Pathogenesis	The organism gains access to the lungs by inhalation followed by hematogenous spread to the brain and meninges. The polysaccharide capsule of <i>C. neoformans</i> inhibits phagocytosis by neutrophils and macrophages in the lungs, promoting dissemination. T-cell-mediated immunity is the primary determinant of resistance.
Laboratory Diagnosis	Diagnosis can be made by culture. Detection of cryptococcal polysaccharide antigen in CSF or serum by latex agglutination is highly sensitive and specific for the diagnosis of cryptococcosis. Direct microscopy of CSF after addition of India ink to delineate the capsule is positive in about 75% of patients with AIDS and 50% of patients without AIDS.
Treatment and Prevention	Amphotericin B plus flucytosine as the initial anti-fungal therapy, followed by a course of fluconazole is used to treat cryptococcal meningitis. Fluconazole is used for suppressive therapy in patients with AIDS. Avoidance by immunocompromised patients of areas with pigeon excreta is a preventive measure.

A 55-year-old man with acute myelogenous leukemia is seen by his medical oncologist because of prolonged neutropenia and fever that developed after chemotherapy despite broad-spectrum antimicrobial therapy. He developed hemoptysis, and lung lesions were apparent on computed tomography scan. Biopsy of one of the lesions showed septate hyphae, and laboratory test results for galactomannan antigen were positive.

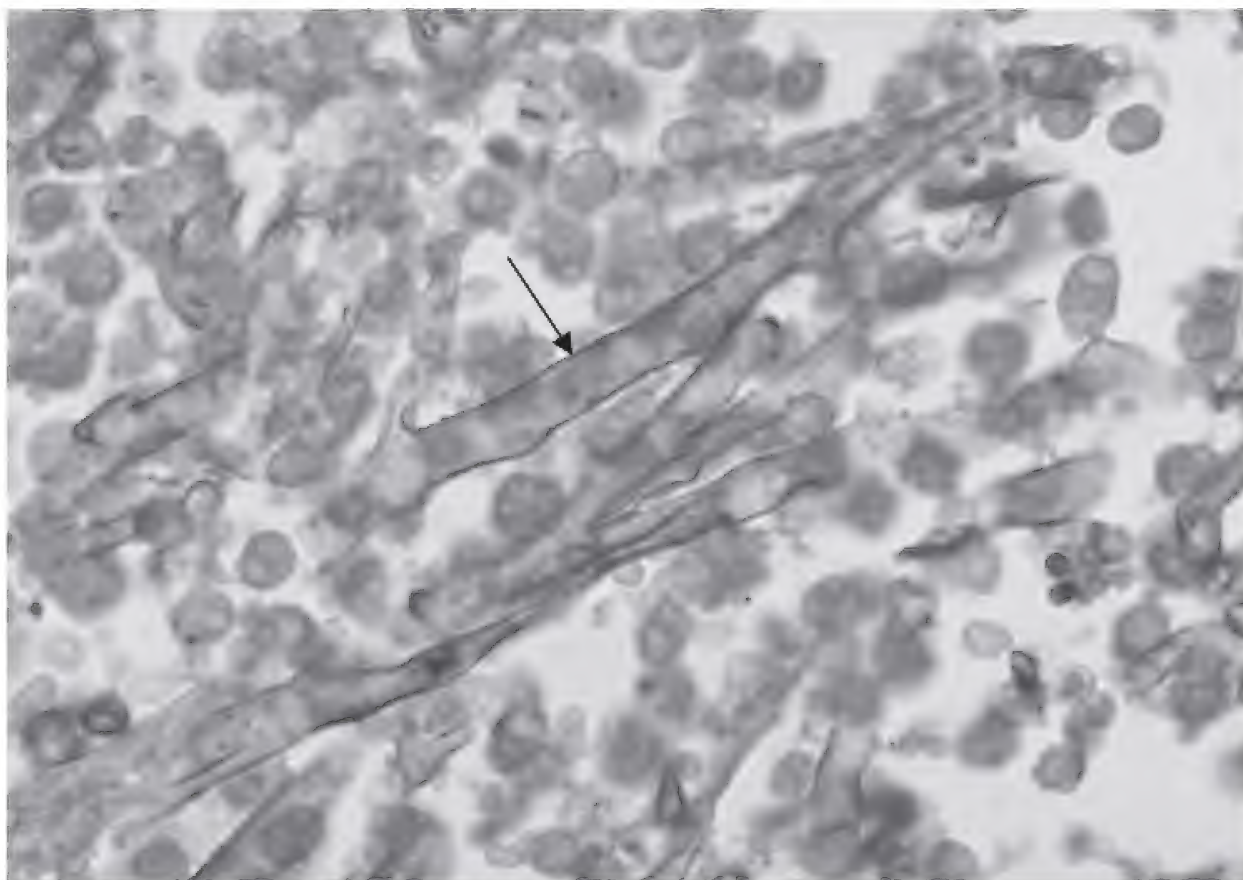


Septate hyphae (Source: Centers for Disease Control and Prevention, Atlanta, GA.)

Aspergillosis

Etiology and Epidemiology	Aspergillosis is caused by <i>Aspergillus</i> species. Aspergillosis is transmitted by the inhalation of aerosolized conidia in soil or dust. Severe, protracted neutropenia is the major risk factor for the development of aspergillosis. Aspergillosis is a common cause of infection and related death in patients with hematologic malignancies.
Clinical Manifestations	In immunocompromised persons, <i>Aspergillus</i> is a common cause of fungal sinusitis and allergic bronchopulmonary aspergillosis characterized by asthma, eosinophilia, and elevated IgE antibodies. <i>Aspergillus</i> can cause a fungus ball (aspergilloma) , a noninvasive mass of hyphae that colonizes an old cavity (eg, a tuberculous cavity) in the lungs of debilitated individuals. Hemoptysis (coughing up blood) is the most common symptom. <i>Aspergillus</i> species can cause invasive pulmonary aspergillosis , which may disseminate to any organ in patients with hematologic malignancies, bone marrow or solid-organ transplant recipients, and in patients receiving high doses of immunosuppressive drugs.
Pathogenesis	Inhaled conidia germinate in the lungs into filamentous hyphae that are angioinvasive, producing hemorrhage, infarction, and necrosis with dissemination to distal sites. The innate cellular defense mechanisms are impaired in underlying disease or with corticosteroid use or with cytotoxic therapy that renders patients neutropenic and susceptible to invasive aspergillosis. Activation of T-cell immunity is critical in the control of infection.
Laboratory Diagnosis	Detection of <i>Aspergillus</i> antigen (galactomannan) in serum by enzyme immunoassay is a useful assay for the diagnosis of invasive aspergillosis. Direct microscopic detection of septate hyphae in tissue biopsy specimens provides a presumptive diagnosis of invasive fungal disease, but culture confirmation is required for identification.
Treatment and Prevention	Therapy for invasive aspergillosis is typically individualized to the patient and may include an extended-spectrum triazole (voriconazole, posaconazole, or isavuconazole) or amphotericin B and/or an echinocandin (micafungin, caspofungin, or anidulafungin). Treatment may also involve surgical debridement.
Notes	

A 55-year-old woman with diabetes is seen in the Emergency Department with severe ketoacidosis. One week after hospital admission, she developed a persistent headache and eye pain. Physical examination revealed an ulcerative lesion on the hard palate, and biopsy results showed “ribbonlike” hyphae on microscopic examination.

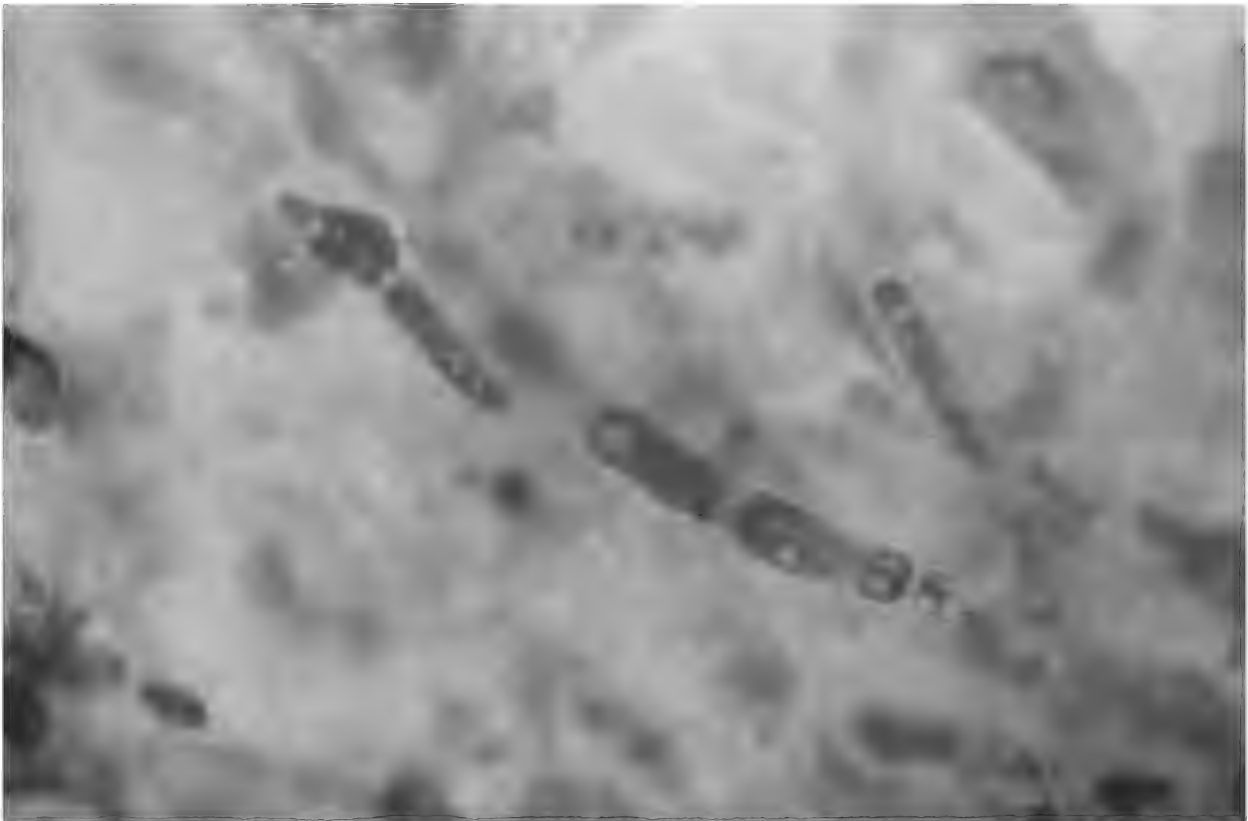


Nonseptate hyphae in biopsy specimen. Arrow points to irregular-shaped, nonseptate hyphae of fungus. (Source: Centers for Disease Control and Prevention, Atlanta, GA.)

Rhizopus Zygomycosis

Etiology and Epidemiology	Zygomycosis (mucormycosis) is a fungal infection caused most commonly by <i>Rhizopus</i> , <i>Absidia</i> , and <i>Mucor</i> species. Zygomycosis is transmitted by the inhalation of aerosolized spores that exist in the soil or on food. Groups at risk for zygomycosis are patients with diabetes with ketoacidosis, individuals with leukopenia, or individuals who are undergoing treatment with immunosuppressive drugs.
Clinical Manifestations	Zygomycosis is characterized by rhinocerebral, pulmonary, or cutaneous disease. Rhinocerebral zygomycosis , most common in patients with diabetes, originates in the paranasal sinus and spreads to the orbit, hard palate, and brain, and has a high mortality rate. Pulmonary and cutaneous zygomycoses are seen in immunocompromised and debilitated individuals and characterized by pulmonary lesions or necrotic skin ulcers often associated with leukemia, organ transplantation, or burns.
Pathogenesis	Inhaled spores germinate in the lung into angioinvasive, filamentous hyphae that result in tissue infarction, necrosis, and hemorrhage. Cell-mediated immunity is the major determinant of resistance to zygomycosis.
Laboratory Diagnosis	Zygomycosis is diagnosed by the detection of nonseptate, "ribbonlike" hyphae in biopsy specimens and confirmed by culture identification.
Treatment and Prevention	Treatment involves a combination of prompt surgical debridement and antifungal therapy with amphotericin B.
Notes	

A 41-year-old woman was seen by an ophthalmologist with physical complaints of unusual eye redness and eye pain. On physical examination, both eyes exhibited corneal inflammation, tearing with discharge, and light sensitivity. A review of office records identified four patients with similar clinical presentations the preceding 2 months. All patients wore soft contact lenses and used a commercially available contact lens solution. Corneal specimens were submitted for microscopic examination and culture.

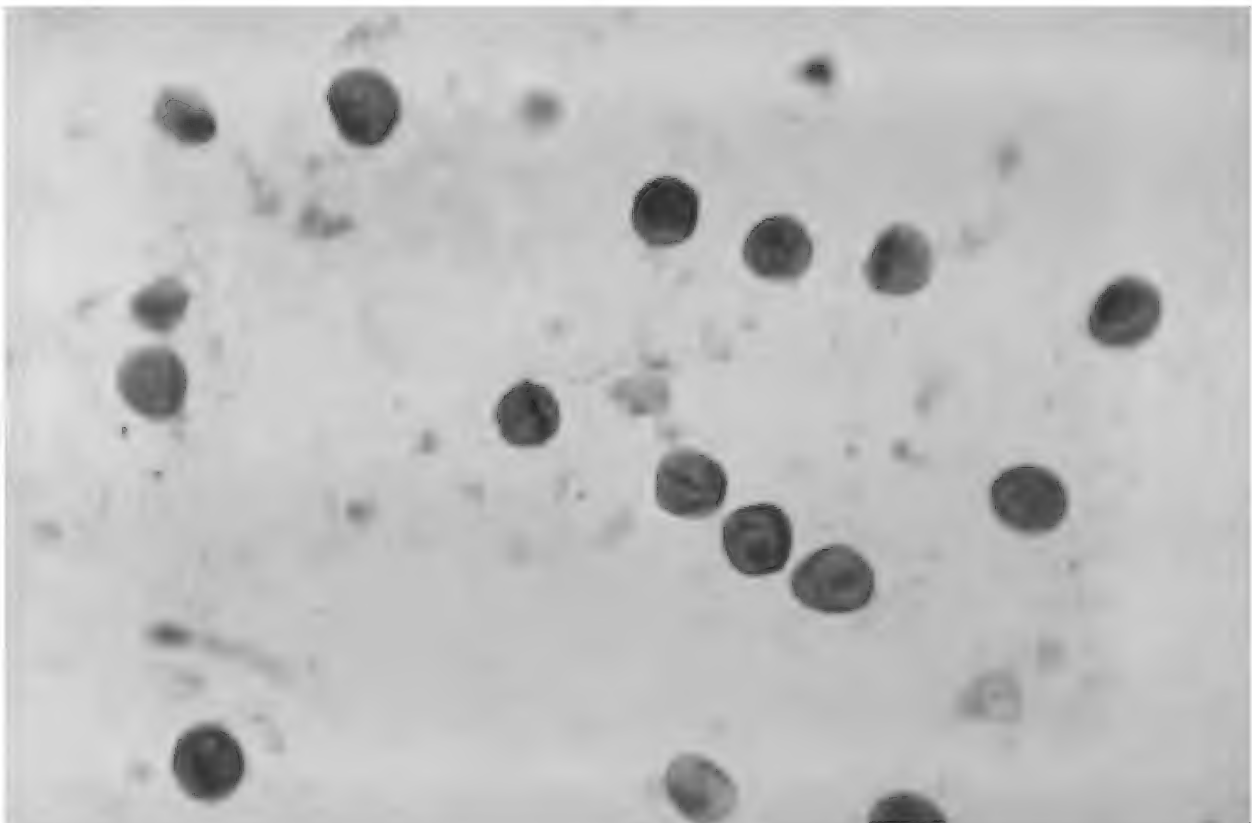


Corneal specimen showing branched, septate hyphae. *Aspergillus* was ruled out. (Source: Centers for Disease Control and Prevention, Atlanta, GA.)

***Fusarium* Keratitis**

Etiology and Epidemiology	<i>Fusarium</i> keratitis is a severe infection of the cornea. Risk factors include trauma, chronic ocular disease, and contact lens use. <i>Fusarium</i> species are opportunistic fungi and a member (along with <i>Scedosporium</i> and <i>Paecilomyces</i>) of the hyalohyphomycosis group that is distinguished by the presence of filamentous hyphae without cell wall pigmentation.
Clinical Manifestations	Keratitis is characterized by eye pain and corneal inflammation accompanied by tearing, discharge, and photophobia. Fusariosis can exhibit a wide range of clinical symptoms, including cutaneous lesions (most common), rhinocerebral syndrome, endophthalmitis, pneumonia, and disseminated infection, particularly in neutropenic, burn, and transplant patients.
Pathogenesis	Histopathology and pathogenesis of <i>Fusarium</i> species is similar to that of aspergillosis. Cell-mediated immunity is the major determinate of resistance to <i>Fusarium</i> species.
Laboratory Diagnosis	Direct examination of tissue biopsy specimens from patients with fusariosis reveals hyphae that resemble <i>Aspergillus</i> . Definitive diagnosis requires culture identification.
Treatment and Prevention	Fusariosis has variable responses to amphotericin B or azoles.
Notes	

A 33-year-old male is seen by his primary care physician with complaints of shortness of breath, fever, and a nonproductive cough. Laboratory workup revealed that the patient was HIV⁺ with a CD4⁺ count of 100, and chest X-ray revealed bilateral infiltrates. Microscopic examination of induced sputum stained with methenamine-silver identified cyst forms of an organism.

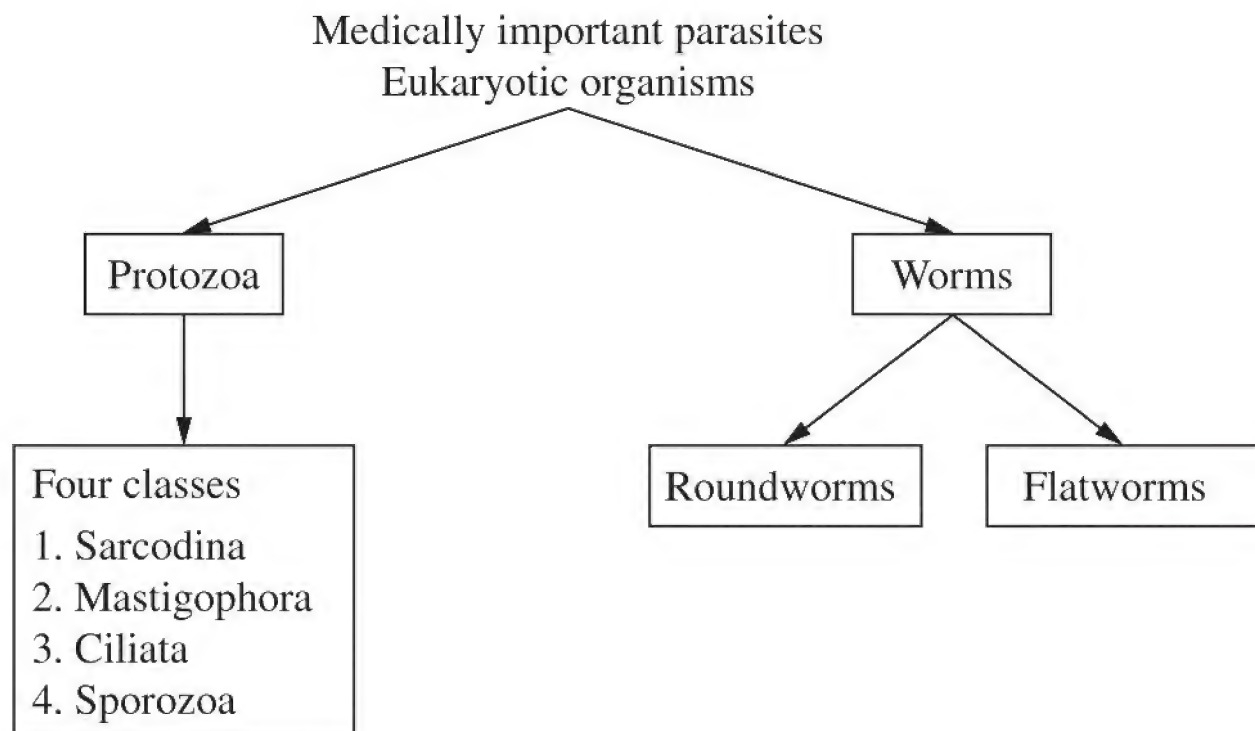


Numerous cysts seen microscopically in induced sputum specimen. (Source: Centers for Disease Control and Prevention, Atlanta, GA.)

Pneumocystosis

Etiology and Epidemiology	Pneumocystis pneumonia (PCP) is a lethal pneumonia of patients with HIV/AIDS caused by <i>Pneumocystis jiroveci</i> (formerly known as <i>P. carinii</i>). <i>P. jiroveci</i> is transmitted by the airborne route, but the reservoir of transmission is unknown. It is classified as a fungus based on nucleic acid and biochemical analyses. The organism is ubiquitous, with more than 80% of individuals seropositive for <i>P. jiroveci</i> antibodies by the age of 4 years. PCP is a common opportunistic infection and leading cause of death in patients with AIDS.
Clinical Manifestations	PCP is characterized by a fever, nonproductive cough, and progressive dyspnea. Extrapulmonary disease occurs in a minority (<3%) of cases involving the lymph nodes, spleen, bone marrow, and liver. PCP is also seen in premature, malnourished infants.
Pathogenesis	<i>P. jiroveci</i> attaches to alveolar pneumocytes, accumulates in the lumen, and induces an inflammatory cell infiltrate, effectively blocking gas exchange in the lung. Cell-mediated immunity is the primary determinant of disease resolution.
Laboratory Diagnosis	Gomori methenamine-silver stain of induced sputum or bronchoalveolar lavage fluid is used to detect morphologic forms of <i>P. jiroveci</i> . Direct fluorescent antibody (DFA) staining is also used for diagnosis.
Treatment and Prevention	PCP is treated with trimethoprim-sulfamethoxazole (TMP-SMX), which is also used prophylactically to prevent PCP in patients with AIDS. In patients who are allergic to sulfa, clindamycin plus primaquine, atovaquone, or pentamidine can be used. Adjunctive glucocorticoids should be given to patients with hypoxemia. Patients should be tested for glucose-6-phosphate dehydrogenase (G6PD) deficiency before taking dapsone or primaquine.
Notes	PCP is an AIDS-defining illness in patients infected with HIV.

CLASSIFICATION



PARASITE CLASSIFICATION

PROTOZOA

There are four classes of protozoan parasites: sarcodina, mastigophora, ciliata, and sporozoa.

- Sarcodina include the **amebae** such as *Entamoeba histolytica* and *Naegleria*

fowleri.

- Mastigophora are commonly known as **flagellates** and include organisms such as *Giardia lamblia*, *Trichomonas vaginalis*, *Leishmania* species, and *Trypanosoma* species.
- Ciliata or **ciliates** have one human pathogen, *Balantidium coli*.
- Sporozoa have alternating sexual and asexual reproductive cycles and include *Plasmodium* species, *Toxoplasma gondii*, *Cryptosporidium parvum*, and *Cyclospora* species.

WORMS

- Roundworms, or **nematodes**, include pathogens such as *Enterobius vermicularis*, *Ascaris lumbricoides*, *Trichuris trichiura*, *Ancylostoma duodenale*, *Necator americanus*, *Strongyloides stercoralis*, *Trichinella spiralis*, *Wuchereria bancrofti*, *Onchocerca volvulus*, and *Toxocara* species.
- Flatworms are either segmented or nonsegmented. The segmented flatworms, or **cestodes**, include a variety of **tapeworms** such as *Taenia solium*, *Taenia saginata*, *Diphyllobothrium latum*, *Echinococcus granulosus*, *Dipylidium caninum*, and *Hymenolepis nana*. The nonsegmented flatworms, or **trematodes**, include a variety of **flukes** including the *Schistosoma* species, *Fasciola hepatica*, *Fasciolopsis buski*, *Paragonimus westermani*, and *Clonorchis sinensis*.

HOSTS, TRANSMISSION, AND LIFE CYCLES

A parasite is an organism that lives upon or within another organism (host) at the expense of that host organism. Some parasites can affect a single host and others require multiple hosts in order to complete their life cycles.

HOST DEFINITIONS

- The **definitive** host harbors the sexually mature or adult form of the parasite.
- The **intermediate** host is required for development to a specific stage. In order to complete its life cycle, the parasite must be transmitted to the definitive host.
- A **reservoir** host is one that parallels the human host.

- A **dead-end** host is one that can no longer transmit the parasite back to a definitive host.
- A **vector**, which is often also a host, is important in transmission from one host to another.

PARASITE TRANSMISSION

Parasite infections are transmitted by one of four different mechanisms.

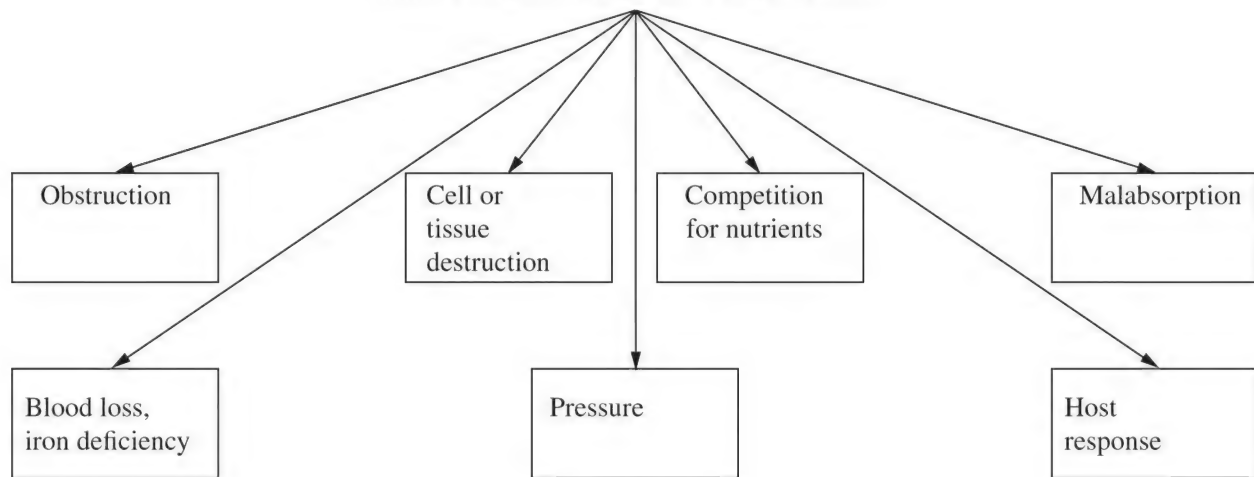
- **Ingestion** of eggs, cysts, or parasites is common for both protozoa and helminths. This usually occurs through fecal contamination of food or water, through direct fecal-oral spread, or through ingestion of intermediate host.
- **Direct skin penetration** by larvae is common in several different nematodes (hookworms and *Strongyloides*) and flukes (schistosomes).
- **Direct person-to-person** spread such as through sexual contact, fecal-oral, or oral-anal contact (eg, *Trichomonas vaginalis*).
- Bites from **arthropod** vectors (eg, *Plasmodium*).

LIFE CYCLES

Many parasites complete their life-cycle in a single host; others require two or more hosts. Parasites that require only a single host can easily be spread through person-to-person contact or through fecal contamination. When multiple hosts are required, infections may be restricted to geographic areas that harbor all hosts. Depending on the parasitic infection, humans can be the definitive host, an intermediate host, or a dead-end host.

MECHANISMS OF PATHOGENESIS

The severity of the pathology is due to seven different mechanisms and is directly related to the parasite load or burden.



PATHOGENIC MECHANISMS

- Physical **obstruction** is common with parasites within the intestine, ducts, and lymphatics. Examples include obstruction of bile ducts by *Ascaris* and obstruction of the lymphatics by *Wuchereria*, which can result in elephantiasis.
- **Cell and tissue destruction** is caused by invasion of host cells by *Plasmodium* resulting in the destruction of erythrocytes.
- **Competition for nutrients** with the host leads to nutrient and vitamin deficiencies. An example is vitamin B12 deficiency associated with the fish tapeworm, *Diphyllobothrium latum*.

NOTES

- **Malabsorption** can occur when large numbers of parasites reside in the intestine.
- **Blood loss and iron deficiencies** occur when parasites attach to intestinal mucosa. Examples include hookworm and whipworm infections.
- **Pressure** can result when a parasite grows within a closed environment such as the CNS.
- The **host immune response** to parasitic infections can result in eosinophilia, tissue destruction, hypersensitivity responses, granuloma formation, and immune complex deposition.

TREATMENT

Because parasites are eukaryotic organisms, treatment relies on differential toxicity. Targeting strategies include preferential uptake, differential susceptibility, or parasite-induced drug modification.

ANTIPARASITIC AGENTS

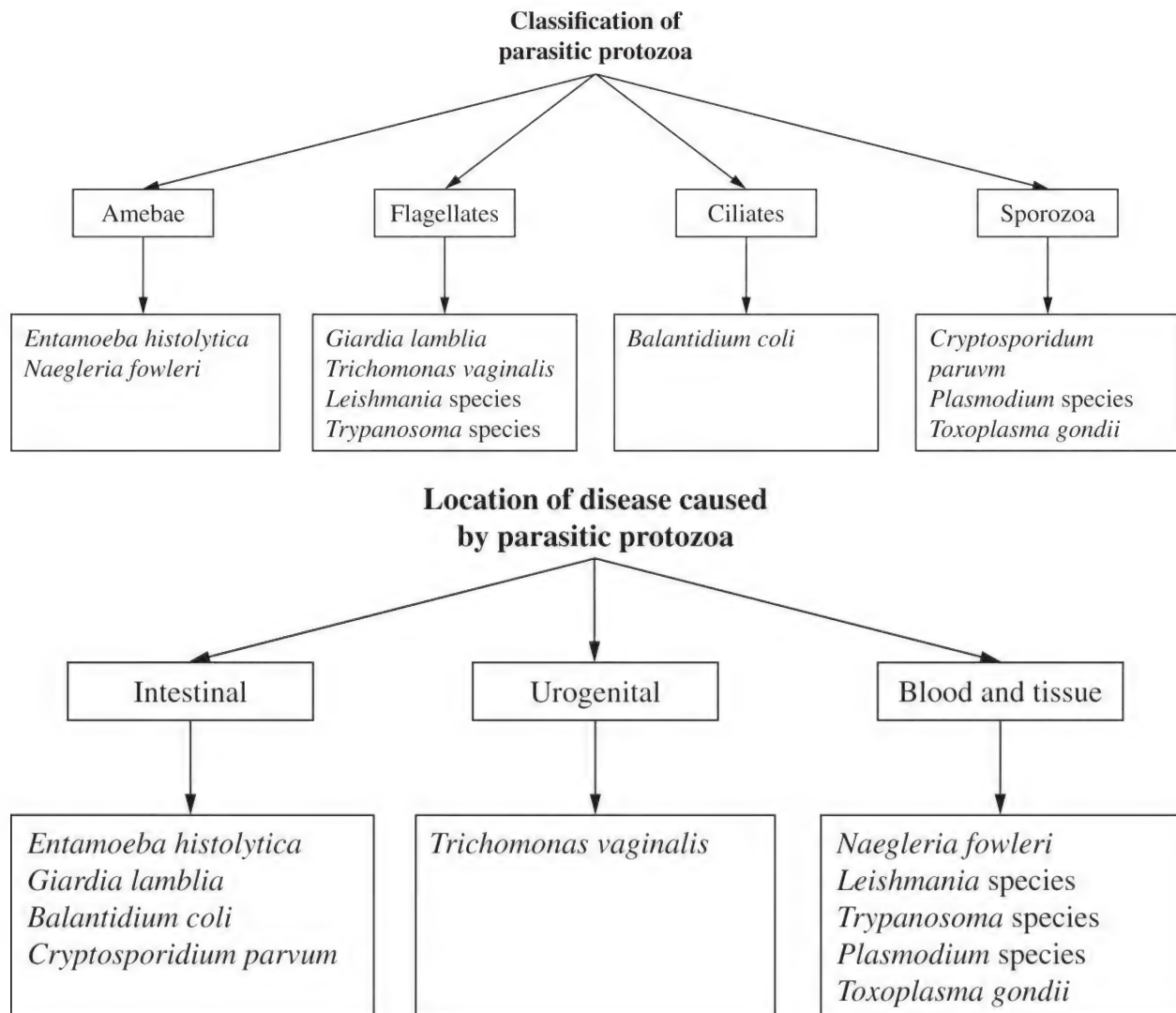
There are seven major classes of antiparasitic drugs.

- Quinolines interfere with DNA replication and are preferentially accumulated in parasitized host cells. Examples include **chloroquine**, **primaquine**, **mefloquine**, **quinine**, and **quinidine**.
- Arsenic and antimonial drugs bind to sulfhydryl groups on proteins and enzymes and target cells with high metabolic activity. Examples include **melarsoprol** (a trivalent arsenical compound) and **sodium stibogluconate** (a pentavalent antimonial compound).
- Folic acid inhibitors target parasites that synthesize their own folic acid for purine biosynthesis. Examples include **pyrimethamine**, **trimethoprim**, and **sulfonamides**.
- Nitroimidazoles (eg, **metronidazole**) act as electron sinks in anaerobic or microaerophilic conditions, depriving the parasite of necessary reducing equivalents such as NADPH. The production of reduced metronidazole by the parasite causes a loss of the helical structure of DNA, strand breakage, and impaired function.

NOTES

- Benzimidazoles are broad-spectrum antihelmintic agents that bind parasite tubulin, thus blocking microtubule assembly and interfering with glucose absorption. Examples include **mebendazole**, **thiabendazole**, and **albendazole**.
- Paralytic agents are effective against many worm infections by causing paralysis (tonic or flaccid depending upon the drug) resulting in expulsion of worms from the host. Examples include **pyrantel pamoate**, **piperazine**, **diethylcarbamazine**, and **ivermectin**.
- Pyrazinoisoquinolines alter the balance of intracellular calcium, causing tetanic muscle contraction and alterations in the parasite tegument, thereby

activating host defenses. An example is **praziquantel**.



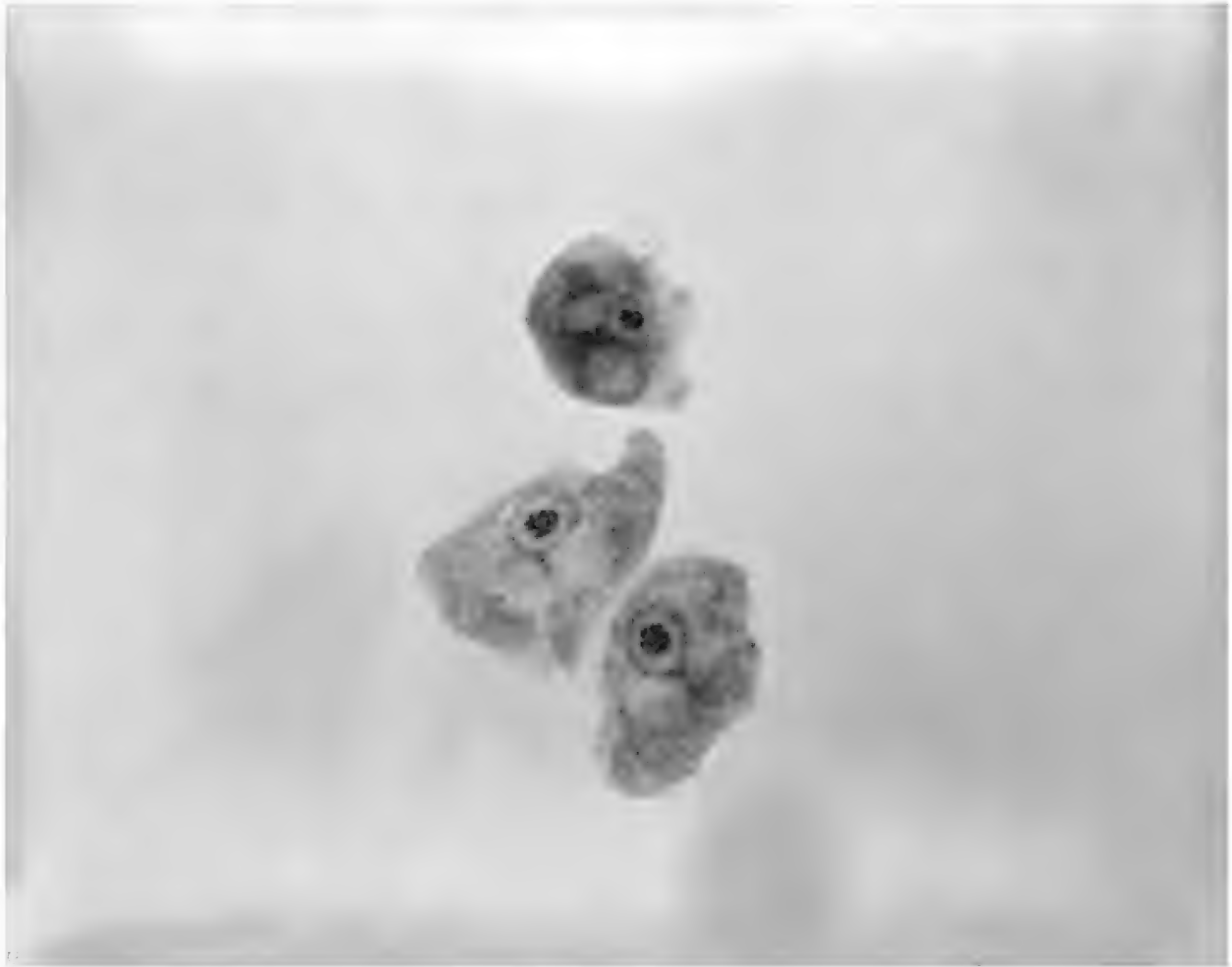
A 34-year-old man from El Paso, Texas visited his internist with complaints of bloody diarrhea, abdominal pain, and tenesmus. History revealed that the patient made regular trips across the border to Mexico where he ate and drank at local bars. A stool sample was collected for microscopic examination and culture. Examination of an iodine-stained wet mount revealed trophozoites

with ingested erythrocytes.

Amebic Dysentery

Organism and Physical Characteristics:	<i>Entamoeba histolytica</i> Two stages are encountered: active amebae (trophozoite stage) is the only form present in tissue, and are also found in fluid feces during amebic dysentery. The inactive cysts are only present in the lumen of the colon and in mushy or formed stools.
Etiology and Epidemiology	Symptomatic and asymptomatic individuals shed cysts in the stool, which can then contaminate food and water. The cysts are resistant to chlorination. Transmission is mainly by fecal-oral and oral-anal spread.
Clinical Manifestations	<i>E histolytica</i> infection results in three different clinical manifestations. In the vast majority of cases, individuals are asymptomatic but remain carriers, shedding cysts in the stool. Symptomatic individuals can exhibit amebic dysentery (cramps, tenesmus, flatulence, and stools containing blood and mucus); a small percentage may experience more serious extraintestinal disease characterized by abscesses , especially in the liver.
Pathogenesis	Upon ingestion of a cyst (metacyst), excystation begins after activation. The metacyst divides rapidly, producing four amebulae (one for each cyst nucleus), each of which divides again to produce eight small trophozoites per infective cyst. Trophozoites infect the large intestine , and may cause tissue destruction and a characteristic flask-shaped ulceration . Further invasion results in abscess formation and systemic spread.
Laboratory Diagnosis	Microscopic examination of stool reveal trophozoites with ingested erythrocytes and cysts with four nuclei. Nonpathogenic species such as <i>Entamoeba coli</i> can be distinguished from <i>E histolytica</i> because <i>Entamoeba coli</i> have cysts containing eight nuclei. Serum antibody tests may be helpful in the diagnosis of amebic dysentery and extraintestinal amebiasis with liver involvement.
Treatment and Prevention	Depending on the severity of symptoms, treatment may include metronidazole and luminal amebicides such as iodoquinol. Control measures: good hygiene, sanitation, and education concerning transmission.

An 18-year-old college freshman is seen in the campus health clinic with complaints of headache, fever, lethargy, and an altered sense of taste and smell. While there, he begins vomiting and becomes disoriented. A lumbar puncture is performed, and examination of the CSF reveals neutrophils and erythrocytes. Latex agglutination tests are negative for a panel of common meningitis-causing bacteria, and a Gram stain of the CSF is negative for any bacterial organisms. Questioning of the roommate revealed that they had gone swimming in a warm freshwater pond 5 days ago. A wet mount of centrifuged CSF reveals the presence of motile trophozoites. The patient is hospitalized and a course of amphotericin B, miconazole, and rifampin begun. The next day the patient slips into a coma and dies 4 days later.

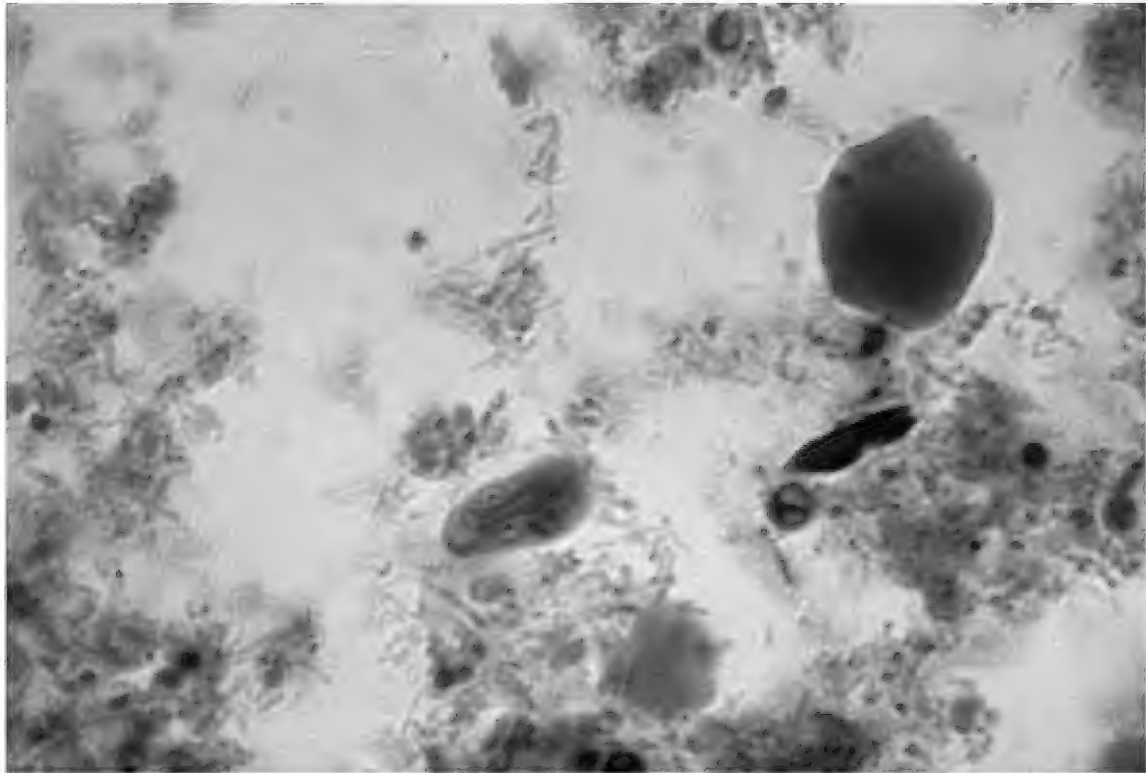


Microscopic examination of wet mount shows motile trophozoites. (Source: Centers for Disease Control and Prevention, Atlanta, GA.)

Primary Amebic Meningoencephalitis

Organism and Physical Characteristics:	<i>Naegleria fowleri</i> A thermophilic, free-living soil ameba. Occurs in three forms: cyst, trophozoite, and a biflagellate. Opportunistic pathogen.
Etiology and Epidemiology	Transmission to humans most often occurs when water containing <i>N fowleri</i> is inhaled through the nose while swimming in warm fresh water.
Clinical Manifestations	<i>N fowleri</i> causes an opportunistic highly fatal meningoencephalitis characterized by rapid onset of fever, stiff neck, headache, disorientation, vomiting, and altered taste and odor sensations. Progression is rapid, leading to coma and death within 4–6 days.
Pathogenesis	The flagellate is inhaled into the nasal cavity during swimming or diving. Once inside the nasal cavity, the flagellated form transforms into a trophozoite. The trophozoites enter through the nasal and olfactory nerve tissue traveling to the brain through the cribriform plate.
Laboratory Diagnosis	Microscopic examination of cerebrospinal fluid reveals neutrophils, erythrocytes, and trophozoites. Amebae can be cultured on a lawn of gram-negative rods, which serve as food for the amebae.
Treatment and Prevention	This is a highly fatal disease with few survivors. Treatment with amphotericin B in combination with rifampin and fluconazole has had some success.
Notes	

Two weeks after returning from a 4-day camping trip, a 13-year-old boy exhibits abdominal pain, watery diarrhea, flatulence, and steatorrhea. After 1 week of symptoms, the boy's mother takes him to their primary care doctor for examination. History reveals that the boy drank water from a mountain stream without first filtering or boiling it. A stool sample is collected and sent to the laboratory for testing. Direct examination reveals pear-shaped trophozoites with two nuclei. He is given a single dose of tinidazole.



Microscopic examination reveals pear-shaped trophozoites with two nuclei. (Source: Centers for Disease Control and Prevention, Atlanta, GA.)

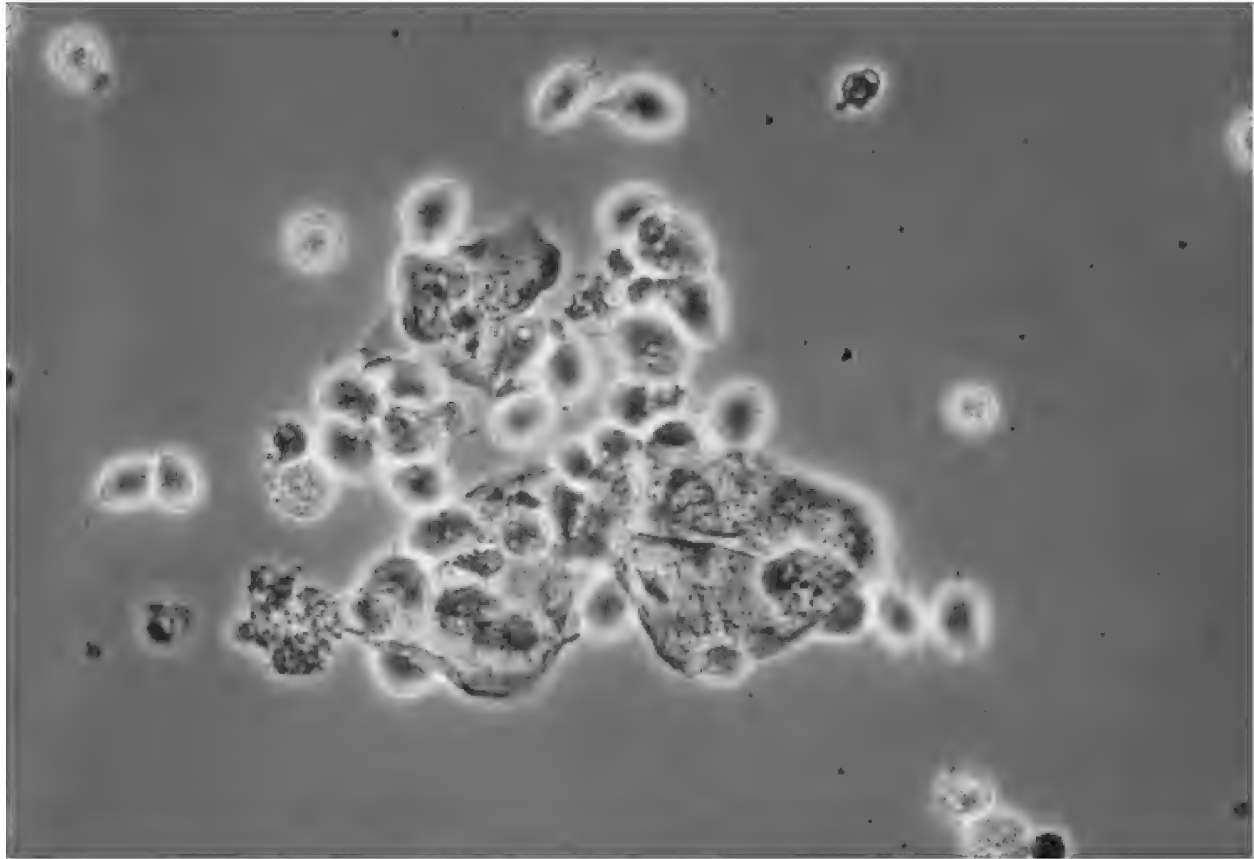
Giardiasis

Organism and physical Characteristics:	<i>Giardia lamblia</i> A flagellated protozoan that exists in trophozoite and cyst forms; infective form is the cyst.
Etiology and Epidemiology	Transmission is by ingestion of cysts, which can occur through fecal contamination of water (community outbreaks) or food, fecal-oral spread (daycare centers) or oral-anal contact (homosexuals). Mountain streams infected by fecal contamination from beavers, muskrats, humans, and other animals are a common source of infection in hikers and campers.
Clinical Manifestations	Symptoms usually occur 1–4 weeks after exposure. Disease ranges from asymptomatic to mild watery diarrhea to a more severe malabsorption syndrome. Asymptomatic individuals may become carriers and shed cysts in the stool. Malabsorption syndrome is characterized by abdominal cramps, foul-smelling stools, flatulence, and steatorrhea (fat in the stool) and can last as long as 4 weeks.
Pathogenesis	Trophozoites attach to epithelial cells in the duodenum and jejunum of the small intestine via their ventral sucking disk. Although they do not invade, they do block absorption, especially of fat.
Laboratory Diagnosis	Cysts containing four nuclei are seen in formed stool from asymptomatic carriers. Trophozoites that are pear shaped with four flagella, two nuclei, and a ventral sucking disk can be found in diarrheal stool. A variety of fecal antigen tests are available as well as the string test, which is used to capture trophozoites from the duodenum when stool results are negative.
Treatment and Prevention	A number of drugs are available to treat giardiasis, including nitroimidazoles (metronidazole or tinidazole), nitazoxanide, benzimidazoles (albendazole or mebendazole), or furazolidone. Paromomycin is recommended for treatment of symptomatic pregnant women. Prevention involves hygiene, education about transmission, and avoidance of infection by filtration, iodination, or boiling water from mountain streams.

Notes

A 24-year-old sexually active woman experiences intense vaginal itching and

burning on urination. She is seen at the health clinic where a pelvic examination reveals the presence of a frothy vaginal discharge, which has a musty odor. Her cervix is friable with diffuse inflammation and covered with numerous petechiae. A wet mount of the vaginal discharge is examined and reveals oval trophozoites that exhibit jerky movement. Metronidazole is prescribed. She is also evaluated for the presence of other sexually transmitted infections.

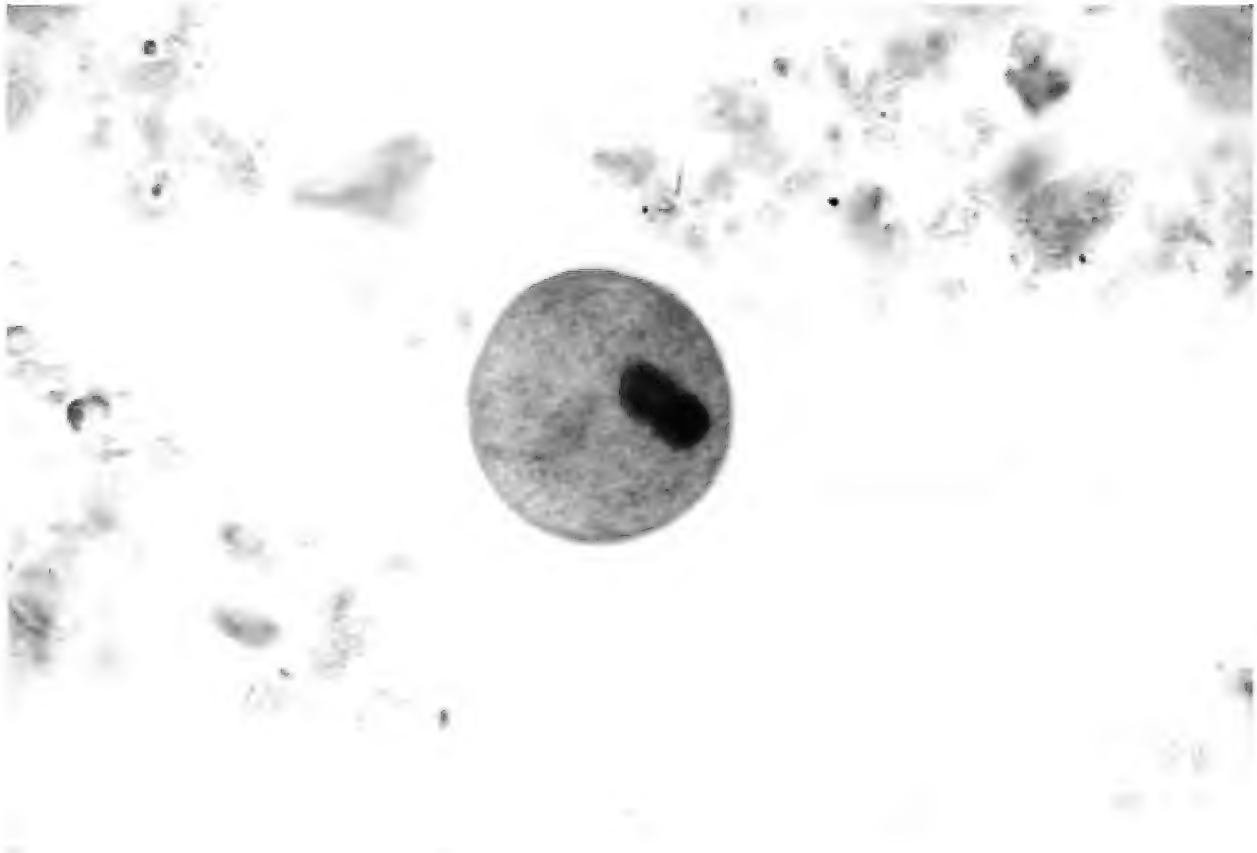


Wet mount of vaginal discharge. (Source: Centers for Disease Control and Prevention, Atlanta, GA.)

Trichomoniasis

Organism and Physical Characteristics:	<i>Trichomonas vaginalis</i> An anaerobic, flagellated protozoan that exists only in the trophozoite form (no cyst stage). It is slightly larger than a granulocyte.
Etiology and Epidemiology	Primarily transmitted by sexual contact. Frequently coexists with other sexually transmitted infections (eg, gonorrhea). Can also be acquired by newborn infants during birth. Trichomoniasis during pregnancy is associated with preterm delivery and low birth weight.
Clinical Manifestations	Frequently symptomatic. In women, the major manifestation is frothy vaginal discharge (vaginitis) and mild vulvovaginal itching. Discharge is greenish yellow and has a musty odor. Symptoms may include vaginal erythema and cervical lesions ("strawberry cervix"). Men are generally asymptomatic but may suffer from urethritis , prostatitis , or epididymitis .
Pathogenesis	Exposure to the trophozoite stimulates a host inflammatory response and epithelial cell destruction.
Laboratory Diagnosis	Oval trophozoites with four anterior flagella that exhibit jerky movement are characteristically seen by microscopic examination of wet mounts. Culture and rapid antigen testing are commonly used.
Treatment and Prevention	Symptomatic women as well as their sexual partners can be treated with antibiotics such as metronidazole or tinidazole. Prevention is best accomplished by following safe sex practices.
Notes	

After returning 1 day previously from the Philippines where he visited several farms that raised pigs, a 30-year-old man exhibits a rapid onset of nausea, vomiting, and watery diarrhea that contains blood and mucus. He visits the Emergency Department where a fresh diarrheal stool sample is collected and sent to the laboratory for ova and parasite examination. Microscopic examination of a saline wet mount reveals the presence of large ciliated trophozoites. The patient is started on a 10-day course of tetracycline.

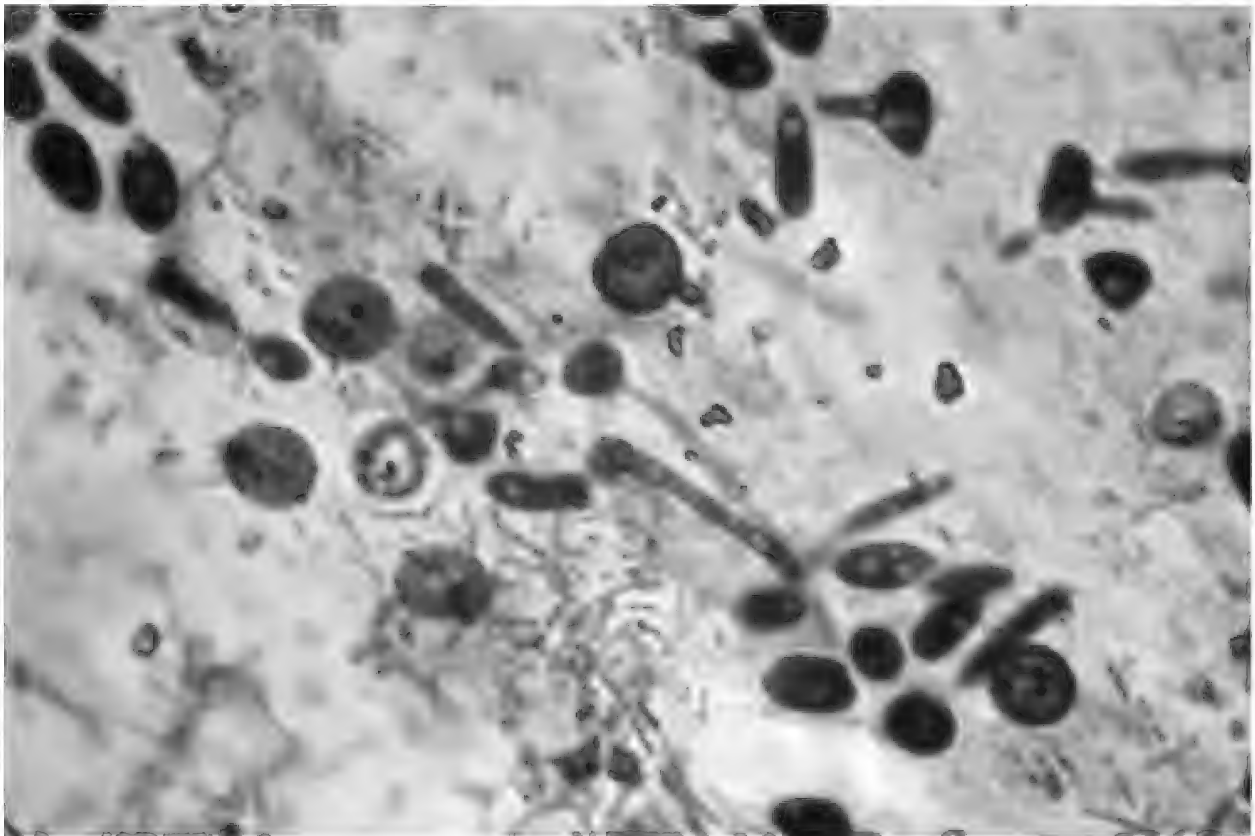


Saline wet mount of diarrheal stool (Source: Centers for Disease Control and Prevention, Atlanta, GA.)

Balantidiasis

Organism and Physical Characteristics:	<i>Balantidium coli</i> The largest and only pathogenic ciliated protozoan known to infect humans. It has two developmental stages: cyst and trophozoite.
Etiology and Epidemiology	Transmission is through ingestion of cyst-contaminated food or water or by fecal-oral spread. Pigs are believed to be the primary reservoir.
Clinical Manifestations	Most human infections are asymptomatic. Acute infection characterized by nausea, vomiting, abdominal discomfort, and watery diarrhea containing blood and mucus similar to that seen with <i>E histolytica</i> .
Pathogenesis	Once ingested, the cyst walls dissolve, and the released trophozoites migrate to the large intestine, cecum and terminal ileum where they feed on bacteria and fecal debris. <i>B coli</i> primarily dwells in the lumen. Rarely, trophozoites invade the mucosa and submucosa of the large bowel and terminal ileum causing abscesses and ulcerations.
Laboratory Diagnosis	Direct examination of formed stool will reveal cysts. Ciliated trophozoites are found in diarrheal stools. Examination must be performed promptly because trophozoites quickly degenerate.
Treatment and Prevention	Tetracycline is the drug of choice. Iodoquinol and metronidazole are alternative drugs.
Notes	

Fourteen children between the ages of 2 and 5 are seen by the same pediatric group for complaints of abdominal cramps, fatigue, and nonbloody, watery diarrhea. Several of the children had a fever and vomiting. All the children attend the same daycare center. Stool samples were collected and subjected to sucrose flotation before staining with a modified Kinyoun acid-fast stain. Upon microscopic examination, acid-fast oocytes are seen in most samples, and an enzyme immunoassay (EIA) test for detecting antigen in the stool is positive in all samples. The treatment prescribed focused on fluid replacement.

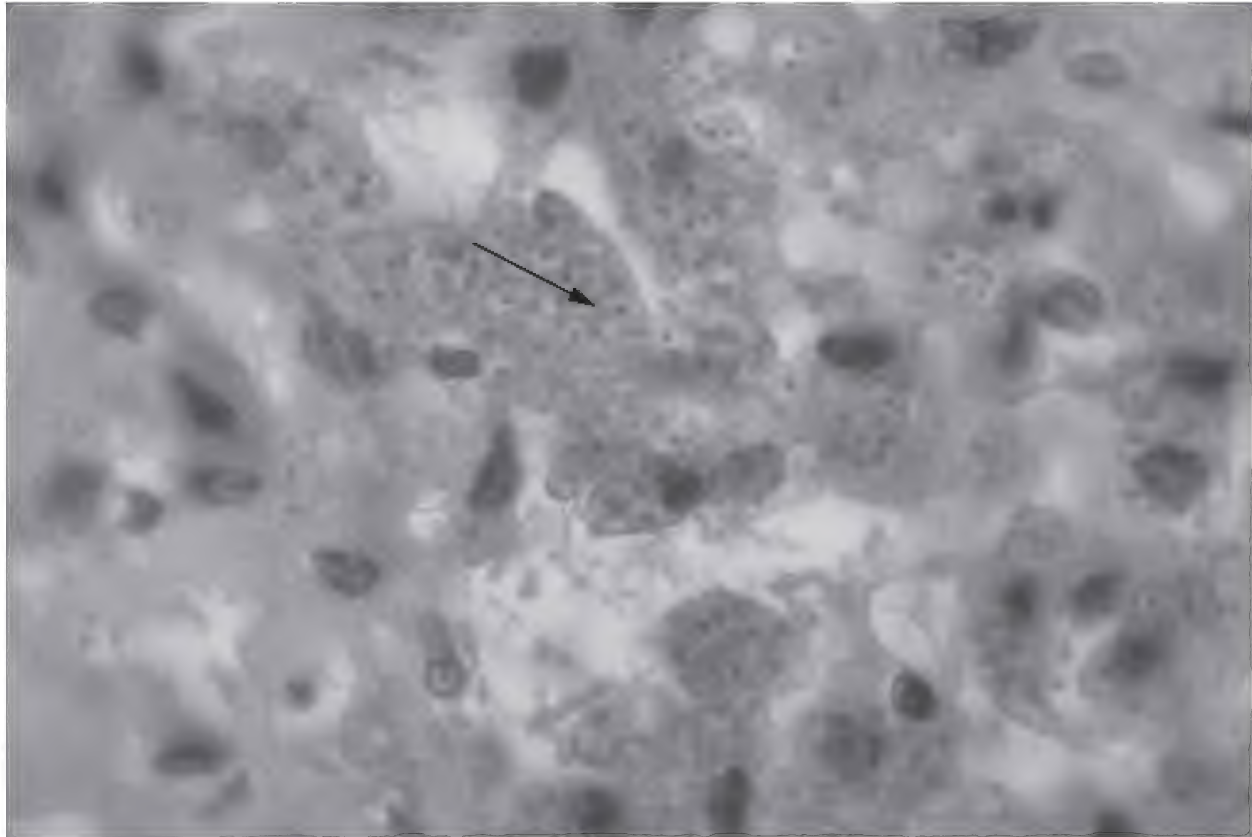


Acid-fast oocytes present in stool sample. (Source: Centers for Disease Control and Prevention, Atlanta, GA.)

Cryptosporidiosis

Organism and Physical Characteristics:	<i>Cryptosporidium parvum</i> Oocyst-forming coccidian protozoa. An obligate intracellular parasite. Oocysts are resistant to all practical levels of chlorination.
Etiology and Epidemiology	A common water-borne disease. Transmission is generally through ingestion of oocyst-contaminated water or person-to-person through fecal-oral or oral-anal routes. The incubation period is 2–14 days.
Clinical Manifestations	<i>C. parvum</i> causes a self-limiting watery diarrhea in individuals with competent immune systems. In immunocompromised individuals (ie, persons with HIV/AIDS or autoimmune disorders), a chronic diarrhea with massive fluid loss may occur resulting in malnutrition, electrolyte imbalance, and wasting. May also infect the respiratory tract.
Pathogenesis	After ingestion of oocysts, sporozoites within the oocyst are released and attach to epithelial cells of the jejunum, where asexual trophozoites form and divide to produce merozoites. Merozoites develop into gametocytes to initiate sexual reproduction. The fertilized zygotes develop into oocysts that are eventually excreted in stool.
Laboratory Diagnosis	Diagnosis involves fecal antigen tests and direct microscopic examination of fecal smears for acid-fast oocysts.
Treatment and Prevention	Treatment for immunocompromised individuals is challenging—supportive measures, fluid replacement, and restoration of the immune system are key measures. If an antimicrobial agent is used, nitazoxanide is a preferred agent. Alternatives are paromomycin and/or azithromycin. Persons with a diagnosis of cryptosporidiosis should not use recreational waters for 2 weeks after symptoms resolve. Boiling water may be necessary to prevent additional cases in water-borne outbreaks.
Notes	

A 43-year-old man living in a rural area in Brazil has extensive nasopharyngeal lesions that have progressed in severity over the last year. A tissue biopsy is examined by acid-fast staining for mycobacteria and found to be negative. A lepromin test is also negative. However, Giemsa staining reveals intracellular nonflagellated amastigotes leading to the diagnosis. A 28-day course of sodium stibogluconate is begun.

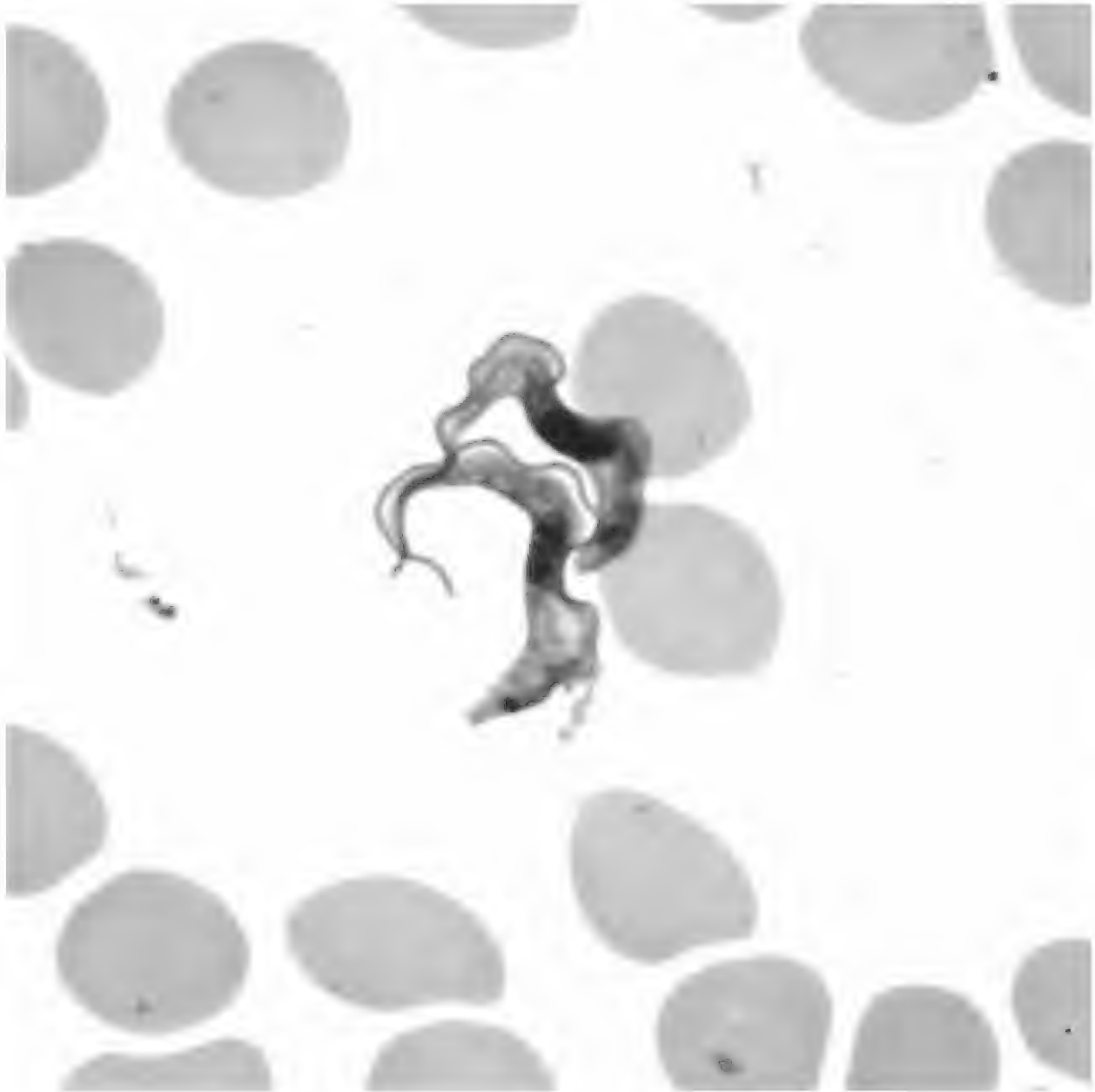


Giemsa-stained tissue biopsy showing intracellular, nonflagellated amastigotes (arrow). (Source: Centers for Disease Control and Prevention, Atlanta, GA.)

Mucocutaneous or Visceral Leishmaniasis

Organism and Physical Characteristics:	<p><i>Leishmania species</i> A genus of trypanosomes. Many different species including <i>L. donovani</i>, <i>L. tropica</i>, <i>L. mexicana</i>, <i>L. infantum</i>, <i>L. major</i>, and <i>L. braziliensis</i>. Invasive blood and tissue flagellate. Two different forms: infective flagellated form (promastigote), found in the alimentary tract of the vector where they are transmitted during feeding, and nonflagellated intracellular form (amastigote). Obligate intracellular parasite of mononuclear phagocytes.</p>
Etiology and Epidemiology	<p>The vector of transmission is the sandfly. Many mammals can serve as reservoirs.</p>
Clinical Manifestations	<p>Three major clinical syndromes: Visceral leishmaniasis (kala azar) is caused by <i>L. donovani</i> (and <i>L. infantum</i>), which invades macrophages that are carried to the liver, spleen, and bone marrow. Disease is characterized by gradual onset of fever, chills, anemia, liver and spleen enlargement, and leukopenia. The disease course is prolonged (months to years) and can result in secondary infections, wasting, and eventual death if left untreated. Cutaneous leishmaniasis (oriental sore or chiclero ulcers) is caused by <i>L. tropica</i>, <i>L. major</i>, and <i>L. mexicana</i> and is characterized by a papule and ulceration at the site of infection. Mucocutaneous leishmaniasis (espundia) is caused by <i>L. braziliensis</i> and starts off as a reaction to the bite. It is a disfiguring disease of soft tissue affecting the nose, mouth, and throat often resulting in secondary infections.</p>
Laboratory Diagnosis	<p>Lymph node aspirates, blood, spleen, liver, or bone marrow puncture (<i>L. donovani</i>), or lymph node aspirates, scrapings, and biopsies from skin lesions (<i>L. tropica</i>, <i>L. mexicana</i>, and <i>L. braziliensis</i>) are examined for amastigote forms. Leishmanin skin tests are positive after recovery but negative during active disease. Serologic tests are also available.</p>
Treatment and Prevention	<p>Drugs for treatment may include amphotericin B, pentavalent antimonials (such as sodium stibogluconate), paromomycin, or miltefosine, depending on the <i>Leishmania species</i> and manifestation of infection. Prevention involves use of insect repellents, minimizing outdoor exposures from dusk to dawn, and physical barriers (fine-mesh bed netting, protective clothing) to prevent bites from sandflies.</p>

A 48-year-old stockbroker returning from a 3-week photo safari in Africa experiences headache, fever, and malaise. Symptoms eventually resolve and then return 6 weeks later. History reveals that he had an ulcerated lesion on his neck during his last week in Africa. A series of blood samples are taken over the next 2 weeks and sent to the laboratory for examination. IgM levels are found to be elevated, and trypanosomes are seen in several of the blood samples. The patient is started on a course of suramin.

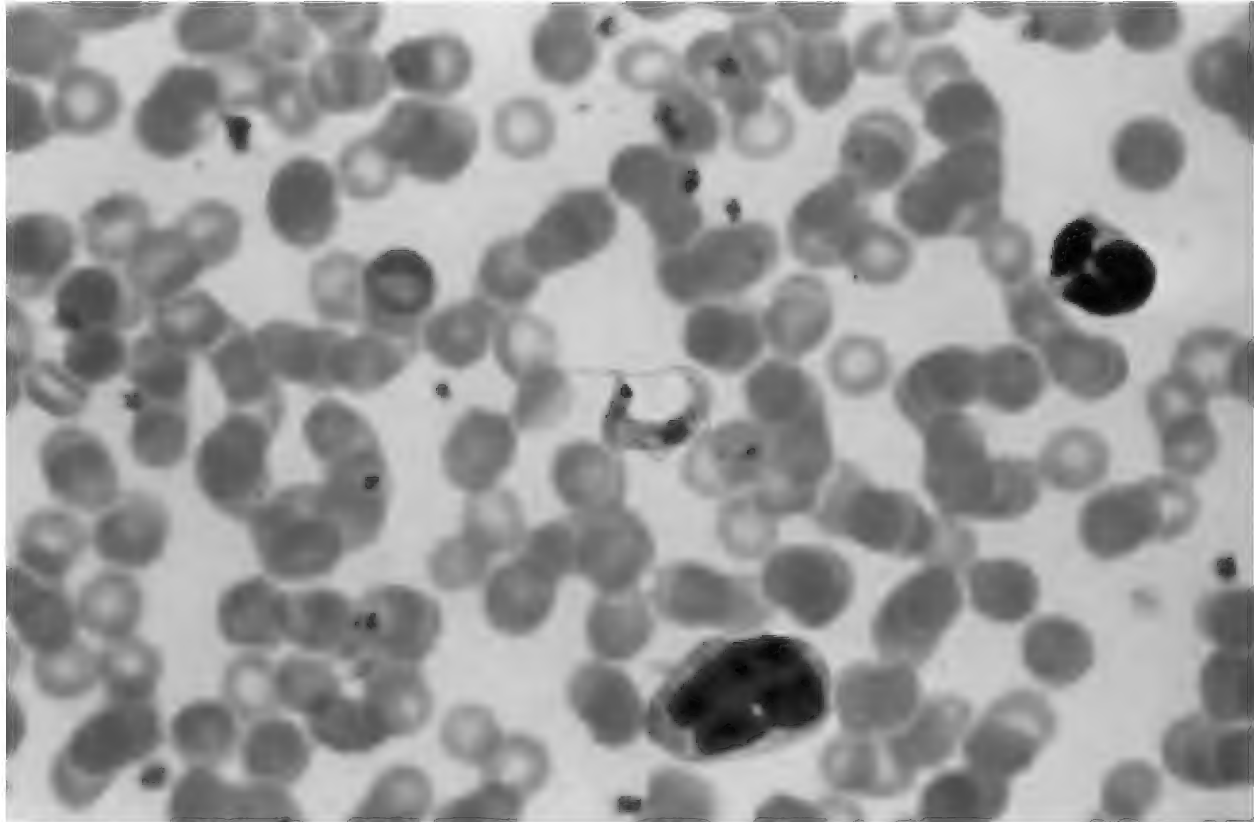


Trypomastigotes in a blood smear (red blood cells = 10 μ m). (Source: Centers for Disease Control and Prevention, Atlanta, GA.)

African Sleeping Sickness

Organism and Physical Characteristics:	<i>Trypanosoma brucei</i> Two subspecies <i>gambiense</i> and <i>rhodesiense</i> , which are indistinguishable morphologically, but differ ecologically and epidemiologically. A hemoflagellate. The only parasitic form in humans is the flagellated trypomastigote.
Etiology and Epidemiology	Humans are the only important reservoirs of <i>T brucei gambiense</i> , which is found in West and Central Africa. In contrast, <i>T brucei rhodesiense</i> has many reservoirs including domestic and wild animals, and is found predominantly in East Africa. The vector of transmission for both is the tsetse fly .
Clinical Manifestations	<i>T brucei gambiense</i> infection is characterized by a cutaneous nodule or chancre at the site of the bite by the tsetse fly, a cyclic fever, and posterior cervical lymph node enlargement (Winterbottom sign) . Systemic illness is chronic (months to years later). Manifestations include demyelinating encephalitis , which can lead to coma and death. The East African form of disease caused by <i>T brucei rhodesiense</i> is more acute, rapidly progressive, and highly fatal.
Pathogenesis	Antigenic variation of surface glycoproteins accounts for the cyclic nature of the fever and effective evasion of the humoral immune system. Access to the CNS occurs through blood.
Laboratory Diagnosis	IgM antibody levels are generally elevated. Diagnosis involves detection of trypomastigotes in blood, cerebrospinal fluid, or fluid aspirated from chancre or lymph node.
Treatment and Prevention	In general, pentamidine or suramin is used for acute disease and melarsoprol is used for CNS involvement. Prevention involves use of physical barriers, protective clothing, and bed netting to minimize tsetse fly bites.

While visiting rural central Mexico with Doctors Without Borders, a 25-year-old fourth-year medical student examines a 6-year-old boy for complaints of fever, headache, and malaise. Physical examination reveals a mild enlargement of the liver and spleen and a furuncle-like lesion on the boy's neck. Giemsa-stained thick and thin blood smears are examined microscopically, and trypanosomes are observed.

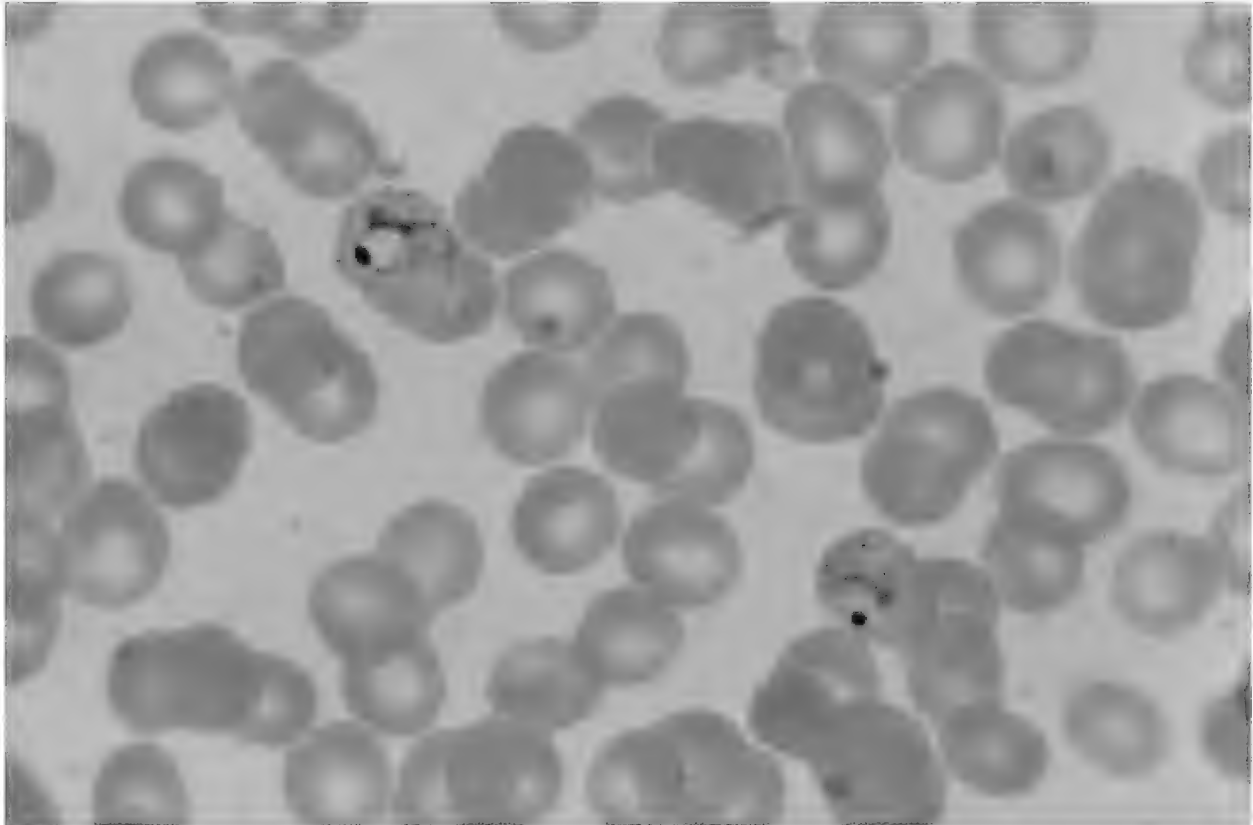


Trypomastigotes in a blood smear (red blood cells = 10 um). (Source: Centers for Disease Control and Prevention, Atlanta, GA.)

American Trypanosomiasis

Organism and Physical Characteristics:	<i>Trypanosoma cruzi</i> Blood and tissue flagellate. Tissue form: amastigote (unflagellated). Blood form: trypomastigote (flagellated).
Etiology and Epidemiology	Mammals and humans serve as reservoirs. The vector is the reduviid bug (<i>Triatoma</i> , "kissing bug"). The infective form (metacyclic trypomastigote) is introduced when infected bug feces, which are deposited when the insect feeds, are rubbed into the conjunctiva, the bite site, or a break in the skin. Disease is seen mainly in Mexico and Central and South America.
Clinical Manifestations	<i>T. cruzi</i> causes American trypanosomiasis (Chagas disease), which is characterized by an erythematous chagoma on the face or arms where the insect bite occurred. If the acute stage of infection occurs around the eye, a unilateral painless periorbital swelling, conjunctivitis, and local lymphadenopathy develops (Romana's sign). Disease is characterized by fever, chills, myalgia, lymphadenopathy, and hepatosplenomegaly that may progress to serious manifestations including meningoencephalitis, myocarditis, megaesophagus, and megacolon.
Pathogenesis	Upon entry into the host, trypomastigotes circulate in blood and are able to infect many different tissues including muscle, heart, and glial cells. Once inside the cell, the amastigote form develops, multiplies, and eventually kills the cell, which results in release of parasites that can now invade other cells.
Laboratory Diagnosis	During the acute disease, trypomastigote forms can be detected in thick and thin blood films. In chronic infections, which are characterized by low-level parasitemia, recovery by culture on special medium or identification by xenodiagnosis, in which a noninfected reduviid bug feeds on the patient and becomes infected, should be undertaken.
Treatment and Prevention	Acute phase disease can be treated with nifurtimox or benznidazole. No effective therapy for chronic cases currently exists. Prevention involves avoiding contact with reduviid insects.
Notes	

One week after returning from a 6-week trip to West Africa, a 22-year-old woman experiences cyclic episodes of chills, fever, and sweats every 48 hours. She is diagnosed with malaria, treated with chloroquine, and recovers. One year later, after residing continuously in Virginia, the symptoms recur. The doctor suspects that her original infection was with *Plasmodium vivax* or *P. ovale* and that hypnozoites latent in her liver have been reactivated. She is treated with primaquine.



Giemsa-stained thin blood film showing intracellular trophozoites (Source: Centers for Disease Control and Prevention, Atlanta, GA.)

Reactivation Malaria

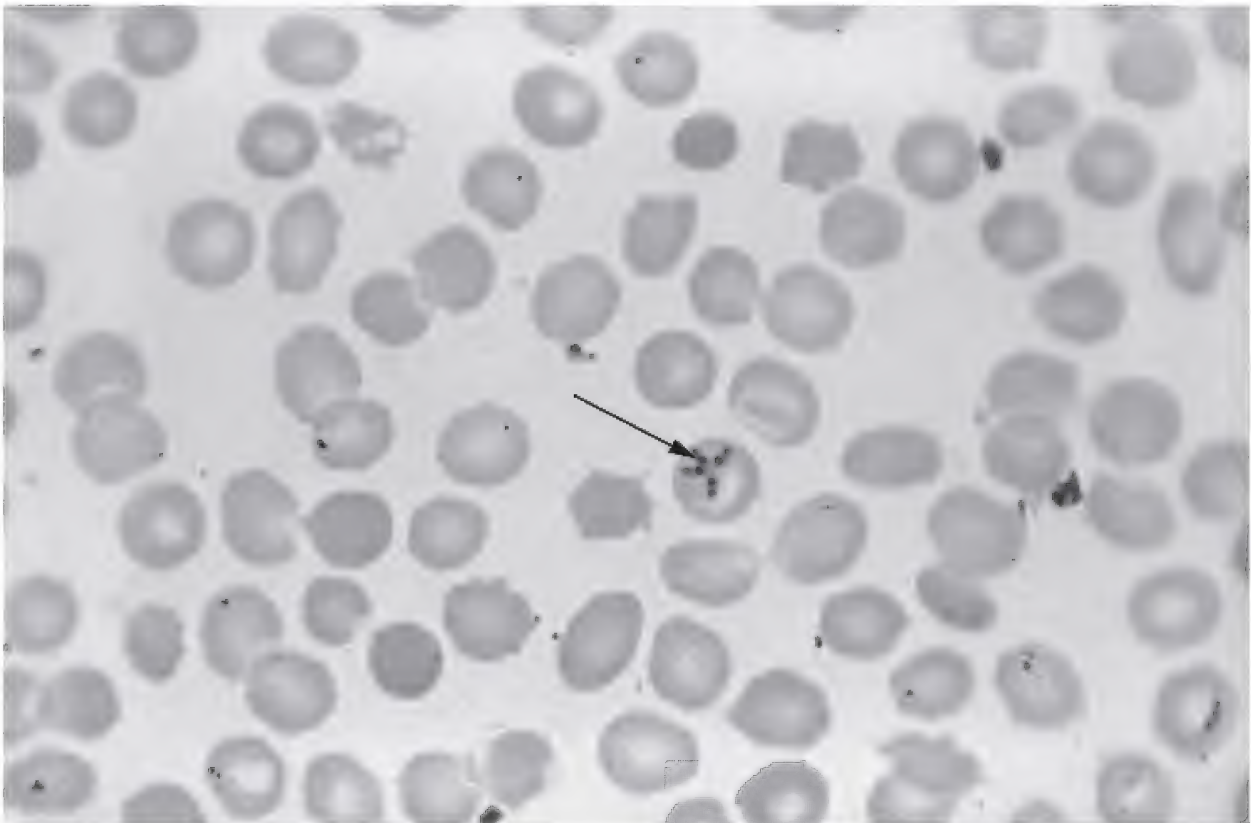
Organism and Physical Characteristics:	<i>Plasmodium species</i> Sporozoan parasite with alternating cycles of sexual and asexual reproduction. Species infecting humans include: <i>P. vivax</i> , <i>P. ovale</i> , <i>P. malariae</i> , and <i>P. falciparum</i> .
Etiology and Epidemiology	The definitive host and vector of transmission is the female <i>Anopheles</i> mosquito. The sexual cycle (called sporogony) occurs in the mosquito host and the asexual cycle (schizogony) occurs in the human intermediate host. <i>P. vivax</i> and <i>P. ovale</i> can form hypnozoites in the liver and remain latent for years.
Clinical Manifestations	Malaria is a cyclic disease with three stages. Shaking chills characterize the “cold stage”; fevers as high as 41°C characterize the “hot stage;” and drenching sweats and exhaustion characterize the “sweating stage.” Other manifestations include splenomegaly, hepatomegaly, and anemia. Disease caused by <i>P. falciparum</i> is more severe and can include capillary occlusion, brain and kidney damage, acute renal failure, and death.
Pathogenesis	Initial infection targets hepatocytes. Hepatocyte schizonts release thousands of merozoites into the bloodstream. <i>P. vivax</i> and <i>P. ovale</i> infect reticulocytes, <i>P. malariae</i> infects mature erythrocytes, and <i>P. falciparum</i> infects all red blood cells (RBCs). The infected RBCs develop a ring trophozoite that forms a schizont with 8–24 merozoites. Rupture of the infected red blood cells causes fever paroxysms.
Laboratory Diagnosis	Each species has characteristic microscopic characteristics that can be observed in thick and thin blood smears.
Treatment and Prevention	Reactivation malaria is caused by <i>P. vivax</i> or <i>P. ovale</i> . Chloroquine is effective against erythrocytic stages if the parasite is susceptible to chloroquine. Primaquine kills latent liver forms, and it kills <i>P. falciparum</i> gametocytes. Chloroquine resistance is common. Thus, treatment of uncomplicated malaria may include an artemisinin-based combination therapy (ACT), atovaquone/proguanil, a quinine-based regimen, or mefloquine. To eradicate the liver stage hypnozoites of <i>P. vivax</i> or <i>P. ovale</i> , primaquine should be administered once fevers have subsided and if the patient does not have glucose-6-phosphate dehydrogenase (G6PD) deficiency. The main way to prevent malaria is by vector control: prophylaxis with an appropriate antimalarial agent (based on prevalence of resistance to antimalarials), bed nets impregnated with insecticide, and mosquito repellents.

A 48-year-old man being treated for colon cancer with an aggressive 6-month three-drug combination chemotherapy regime begins to experience fever, headache, confusion, and seizures. He has had several indoor cats as pets for the last 20 years. A diagnosis is made based on characteristic clinical and radiographic findings. The patient is treated with a combination of pyrimethamine and sulfadiazine.

Reactivation Toxoplasmosis

Organism and Physical Characteristics:	<i>Toxoplasma gondii</i> An obligate intracellular parasite belonging to the apicomplexan class Conoidasida. Worldwide in distribution.
Etiology and Epidemiology	Three different routes of transmission: ingestion of undercooked cyst-contaminated meat, exposure to oocysts in cat feces, and via transplacental spread. Cats are the definitive host and humans, as well as other animals, serve as intermediate hosts.
Clinical Manifestations	Acute infection is asymptomatic in 80%–90% of healthy adults. When symptomatic, acute disease resembles mononucleosis. Congenital infections may be asymptomatic or severe with serious and progressive visual, hearing, motor, and cognitive problems in a child. Premature birth, spontaneous abortion, and stillbirths occur. A common cause of intraocular inflammation and posterior uveitis in immunocompetent patients. In immunocompromised individuals, reactivation disease may include encephalitis and multifocal CNS lesions.
Pathogenesis	After infection with the cyst form, trophozoites develop and invade the intestinal wall, where they are engulfed by macrophages. The trophozoites survive and multiply in macrophages, circulate, and enter many different tissues, where they form oocysts that can remain viable for years. Transplacental spread of trophozoites occurs during acute infection.
Laboratory Diagnosis	Serology, the finding of trophozoites during the acute phase, and examination of tissue biopsy specimens for cysts are used in diagnosis.
Treatment and Prevention	In general, a combination of pyrimethamine and sulfadiazine are used to treat reactivation and congenital disease. Antibodies can protect against transplacental spread. Spiramycin can be used to prevent transmission from infected mother to fetus. Pregnant women should avoid cat litter boxes. Prevention also involves proper cooking of meat.

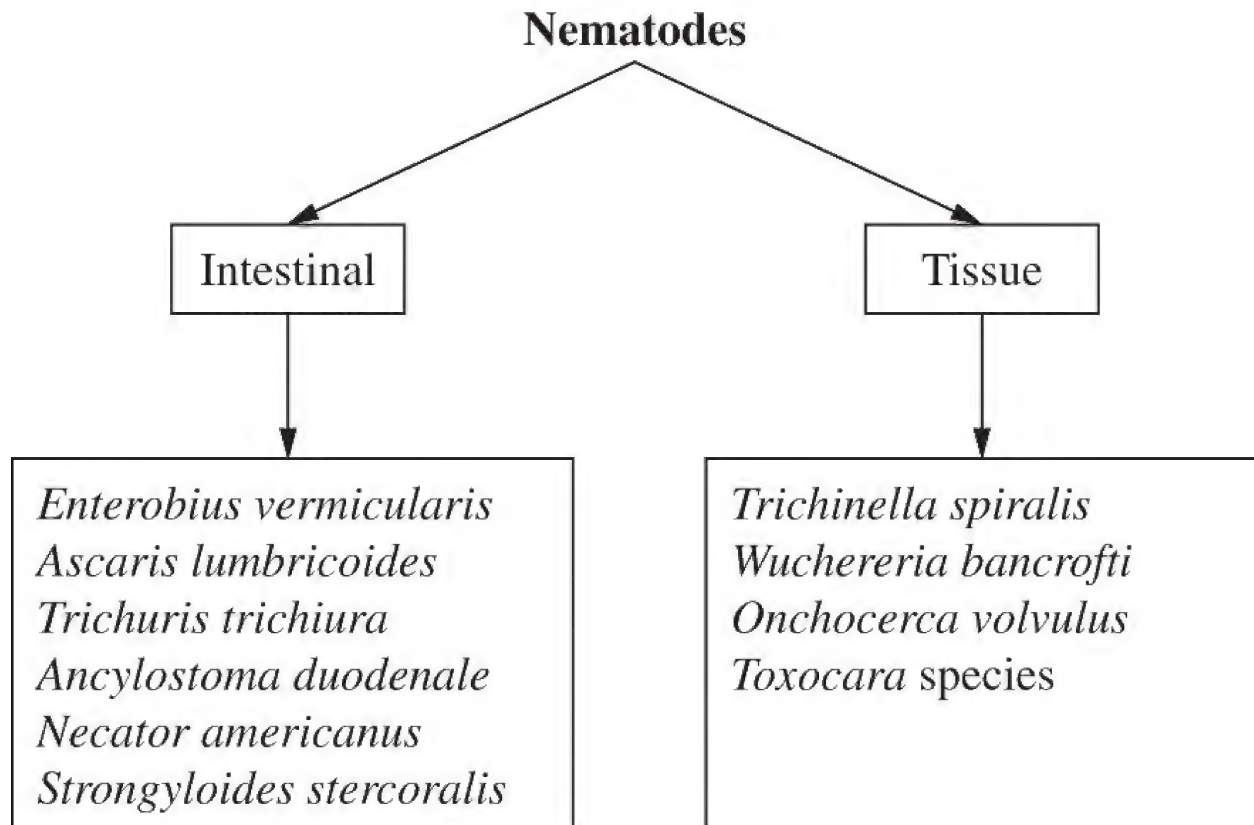
A 65-year-old woman who lives in Maryland presents to the Emergency Department with severe fatigue, generalized weakness, high fevers, chills, and sweats. She has a history of rheumatoid arthritis and had been started on immune modulatory therapy (antibody blockade of tumor necrosis factor-alpha) a few months ago. She just returned from a 2-week summer vacation on Nantucket Island. Physical exam reveals a fatigued and ill-appearing woman with a fever of 40°C. Clinical laboratory work-up reveals evidence of severe hemolytic anemia, elevated creatinine, and elevated liver enzymes.



Giemsa-stained thin blood film showing intracellular parasites. (Source: Centers for Disease Control and Prevention, Atlanta, GA.)

Babesiosis

Organism and Physical Characteristics:	<i>Babesiosis</i> is a tick-borne infection caused by sporozoan parasites of the genus <i>Babesia</i> with <i>Babesia microti</i> being the predominant etiologic species. Infects and lyses the host red blood cells.
Etiology and Epidemiology	Transmission is through exposure to infected ticks (<i>Ixodes scapularis</i>) or, less commonly, through blood transfusion, or through maternal-fetal transmission. Babesiosis is endemic in the northeastern United States, especially in New England and Cape Cod and nearby islands (eg, Nantucket Island, Martha's Vineyard), as well as the Upper Midwest region of the United States and in Europe.
Clinical Manifestations	Incubation period is 7–10 days after a tick bite. Symptoms typically include fatigue/malaise, generalized weakness, high fevers, chills, and sweats. Other symptoms may include loss of appetite, nausea, myalgias, and arthralgias. Severe babesiosis can include complications such as ARDS, renal failure, jaundice with markedly elevated liver enzymes, disseminated intravascular coagulation (DIC), congestive heart failure. Risk factors for more severe disease include: age >50 years old, asplenism, immunosuppression due to treatment of cancer or organ transplantation, immune modulatory therapy (eg, antibody blockade of tumor necrosis factor-alpha), or HIV/AIDS. Clinical laboratory findings may reveal evidence of hemolytic anemia, hyperbilirubinemia, thrombocytopenia, elevated creatinine, elevated liver enzymes.
Pathogenesis	<i>Babesia</i> invade and lyse host red blood cells, causing hemolytic anemia in some cases.
Laboratory Diagnosis	Diagnosis is made by microscopic examination of thin blood smears stained with Wright's or Giemsa to identify parasitemia. A tetrad arrangement of parasites in a red blood cell may appear as a " Maltese Cross ." Diagnosis also can be made with serology by indirect immunofluorescence antibody testing or by PCR assay.
Treatment and Prevention	Treatment consists of atovaquone plus azithromycin, or quinine plus clindamycin. Prevention involves containing and eliminating the vectors and prompt removal of ticks.



KEY CONCEPTS

- Pathogenesis relates to the worm load, destructive migration, and host inflammation.
- Transmission includes ingestion of eggs or larvae, arthropod bites, and direct skin penetration.

SUMMARY OF NEMATODE TRANSMISSION

Ingestion of Eggs	Ingestion of Larvae	Direct Skin Penetration by Larvae	Mosquito or Fly Vectors
<i>Enterobius vermicularis</i> , <i>Ascaris lumbricoides</i> , <i>Trichuris trichiura</i> , <i>Toxocara</i> species	<i>Trichinella spiralis</i>	<i>Ancylostoma duodenale</i> , <i>Necator americanus</i> , <i>Strongyloides stercoralis</i>	<i>Wuchereria bancrofti</i> , <i>Onchocerca volvulus</i>

A 2-year-old girl has been having trouble sleeping because of intense perianal itching. Her mother takes her to the pediatrician for examination. The pediatrician instructs the mother to obtain a perianal specimen that night using an applicator covered with transparent scotch tape sticky side out. The specimen is examined microscopically, revealing characteristic eggs. A prescription for pyrantel pamoate is given to the entire family and the pediatrician requests that she come back in 2 weeks for examination before a second course is started.



A Scotch tape test reveals a characteristic egg. (Source: Centers for Disease Control and Prevention,

Atlanta, GA.)

Pinworm Infection (Enterobiasis)

Organism and Physical Characteristics:	<i>Enterobius vermicularis</i> Nematode (roundworm). Intestinal.
Etiology and Epidemiology	<i>E. vermicularis</i> is the causative agent of pinworm infection, which is the most common nematode infection in the United States. Transmission is through ingestion of eggs either by fecal-oral spread or by swallowing dust containing eggs. Autoinfection can occur by fecal-oral route. Retroinfection occurs when larvae develop in the perianal area and then migrate back through the rectum.
Clinical Manifestations	The major symptom is pruritus ani leading to intense scratching and secondary bacterial infections. Urethritis, vulvovaginitis, salpingitis, or pelvic peritonitis may occur from aberrant migration of the adult worm from the perineum.
Pathogenesis	Following ingestion, eggs hatch in the small intestine and larvae migrate to the colon where they differentiate into adults. The adult gravid female migrates from the colon out the anus at night to lay eggs in the perianal area. The eggs are infectious after a few hours.
Laboratory Diagnosis	Eggs are recovered for diagnosis by perianal sampling using an applicator covered with transparent adhesive tape (sticky side out). Eggs are generally not found in stool samples.
Treatment and Prevention	Pyrantel pamoate or a benzimidazole (albendazole or mebendazole) can be used to kill adult worms. Because the life cycle lasts 2 weeks, a second dose is given at that time to prevent reinfection. All family members should be treated. Prevention involves good personal hygiene and prompt treatment.

A 10-year-old boy has been experiencing chronic abdominal discomfort. He is brought to the clinic exhibiting a fever of 38.9°C. During examination, a worm 20 cm in length begins to emerge from the patient's nose. A stool sample is collected that shows several worms as well as many oval eggs with a knobby surface.



Egg with characteristic bumps observed in stool sample. (Source: Centers for Disease Control, Atlanta, GA.)

Ascaris lumbricoides Infection

Organism and Physical Characteristics:	<i>Ascaris lumbricoides</i> Largest of the human intestinal nematodes. Intestinal.
Etiology and Epidemiology	The most common nematode infection in humans. <i>A. lumbricoides</i> is large, reaching lengths of 20–35 cm. Transmission is through ingestion of eggs found in soil or food contaminated by human feces. Eggs embryonate after incubation of several weeks in the soil.
Clinical Manifestation	The severity of symptoms is dependent on the worm load or burden. Acute transient pneumonitis is a symptom resulting during the migration of larvae to the lungs. Bowel obstruction and malnutrition can result from large worm burdens in the intestine. Peritonitis secondary to bowel perforation, blockages of ducts, or occlusion of the appendix can result when adult worms migrate.
Pathogenesis	Eggs hatch in the small intestine. Rhabditiform larvae penetrate the wall of the duodenum and are transported passively by portal blood to the liver and subsequently to the lungs resulting in pneumonitis and eosinophilia. The larvae penetrate alveoli where they grow and molt, pass from the respiratory system to be coughed up and swallowed and thus returned to the small intestine. The adult worm remains in the intestine, matures to an adult female or male worm. After fertilization, the female lays eggs that are passed in the stool. The worms do not attach, but rather stay in place through constant movement. When the human host has a fever, or is treated with antibiotics, the worms migrate and lodge in ducts, which can result in obstruction.
Laboratory Diagnosis	Diagnosis is usually through the finding of eggs or adult worms in stool. The eggs are oval with a knobby surface. The eggs can persist in soil for years. During the lung migration, sputum samples may reveal larvae and eosinophils.
Treatment and Prevention	Treatment is with pyrantel pamoate or a benzimidazole (albendazole or mebendazole). Prevention involves proper human waste disposal and personal hygiene.

A 7-year-old malnourished girl living in rural Alabama presents with abdominal cramps, bloody diarrhea with mucus, and tenesmus. A blood sample reveals the child is anemic. A stool culture is negative for *Shigella*; however, direct examination of the stool reveals the presence of barrel-shaped

eggs with a plug on each end. She is started on a course of mebendazole.



Eggs (50 μ m) with a distinctive polar plug. (Source: Centers for Disease Control and Prevention, Atlanta, GA.)

Trichuriasis (Whipworm Infection)

Organism and Physical Characteristics:	<i>Trichuris trichiura</i> Nematode (roundworm). Also, known as whipworm. Adult worms have a thread-like anterior end that is imbedded in the mucosa of the large intestine.
Etiology and Epidemiology	Transmission is through ingestion of eggs from soil contaminated with human feces. Adult females produce 3,000 to 10,000 eggs per day that are passed in stool. They become infectious after incubating for 2–3 weeks in the soil. Parasite has a worldwide distribution including areas of the rural southeastern United States. Use of human feces as fertilizer contributes to infection and spread.
Clinical Manifestations	Symptoms vary depending on the worm burden. Small burdens are often asymptomatic . With larger worm loads, symptoms develop that include abdominal pain, bloody diarrhea, tenesmus, rectal prolapse, anemia , and eosinophilia along with nutritional and weight loss. In severe cases, significant blood loss can occur.
Pathogenesis	After ingestion, eggs hatch in the small intestine. Larvae penetrate the villi where they continue to develop. The young worms move to the cecum and penetrate the mucosa, where they mature into adults. The adult forms attach to the colon, causing local ulceration. They can live 4–8 years during which time females can lay thousands of eggs per day.
Laboratory Diagnosis	Characteristic barrel-shaped eggs with a plug on each end can be found on direct examination of stool or by using concentration techniques.
Treatment and Prevention	A benzimidazole (mebendazole or albendazole) can be used for treatment. Prevention involves proper disposal of human fecal material and good personal hygiene.
Notes	

A 10-year-old girl living in rural Georgia is taken to a medical clinic with abdominal pain, diarrhea, bloating, and nausea. Questioning of the mother reveals that the abdominal pain is exacerbated by meals and that the child rarely wears shoes when playing outside. A stool sample is collected and microscopic examination reveals the presence of characteristic eggs.



Microscopic examination of the stool sample reveals the presence of thin-shelled eggs. (Source: Centers for Disease Control and Prevention, Atlanta, GA.)

Hookworm Infection

Organism and Physical Characteristics:	<i>Ancylostoma duodenale</i> (Old World hookworm) and <i>Necator americanus</i> (New World hookworm) Both are nematodes (roundworms) with a similar life cycle. Intestinal. Also called hookworm. Humans are the major reservoir.
Etiology and Epidemiology	Eggs hatch in soil as rhabditoid larvae; develop into infective filariform larvae in soil where they can persist for weeks to months. Infection occurs by direct skin penetration of filariform larvae. Larvae are carried by the blood to the heart and then to the lungs. They penetrate into the pulmonary alveoli and ascend the bronchial tree to the pharynx. They are swallowed and end up in the small intestine, where they develop into adult worms that can live 5–15 years and produce thousands of eggs per day. The eggs are then passed in stool, contaminate soil, and hatch to continue the cycle.
Clinical Manifestations	Most individuals are asymptomatic , but some people will develop an allergic rash at the site of entry or pneumonitis during the larval lung migration. Heavy worm burdens may result in anemia, weight loss, fatigue, and mental or physical retardation. Chronic infection is a cause of microcytic hypochromic anemia .
Pathogenesis	Pathogenesis directly related to worm burden. Adult worms feed on blood, which can result in blood loss as high as 30 μ L per worm per day and resultant anemia. Pneumonitis and eosinophilia are associated with the larval lung migration.
Laboratory Diagnosis	Microscopic demonstration of hookworm eggs in feces is diagnostic.
Treatment and Prevention	A benzimidazole (mebendazole or albendazole) or pyrantel pamoate is used to kill hookworm. Prevention involves wearing shoes, education about transmission, and proper human waste disposal.

A 6-year-old girl living in rural eastern South Carolina, presents with abdominal pain, distension, vomiting, and diarrhea that consists of voluminous mucoid stools. Microscopic examination of a fresh stool specimen reveals the presence of characteristic larvae. Questioning of the father reveals that the girl often plays outside barefoot. The patient is started on a course of ivermectin and told to come back in 3 days for a second dose.

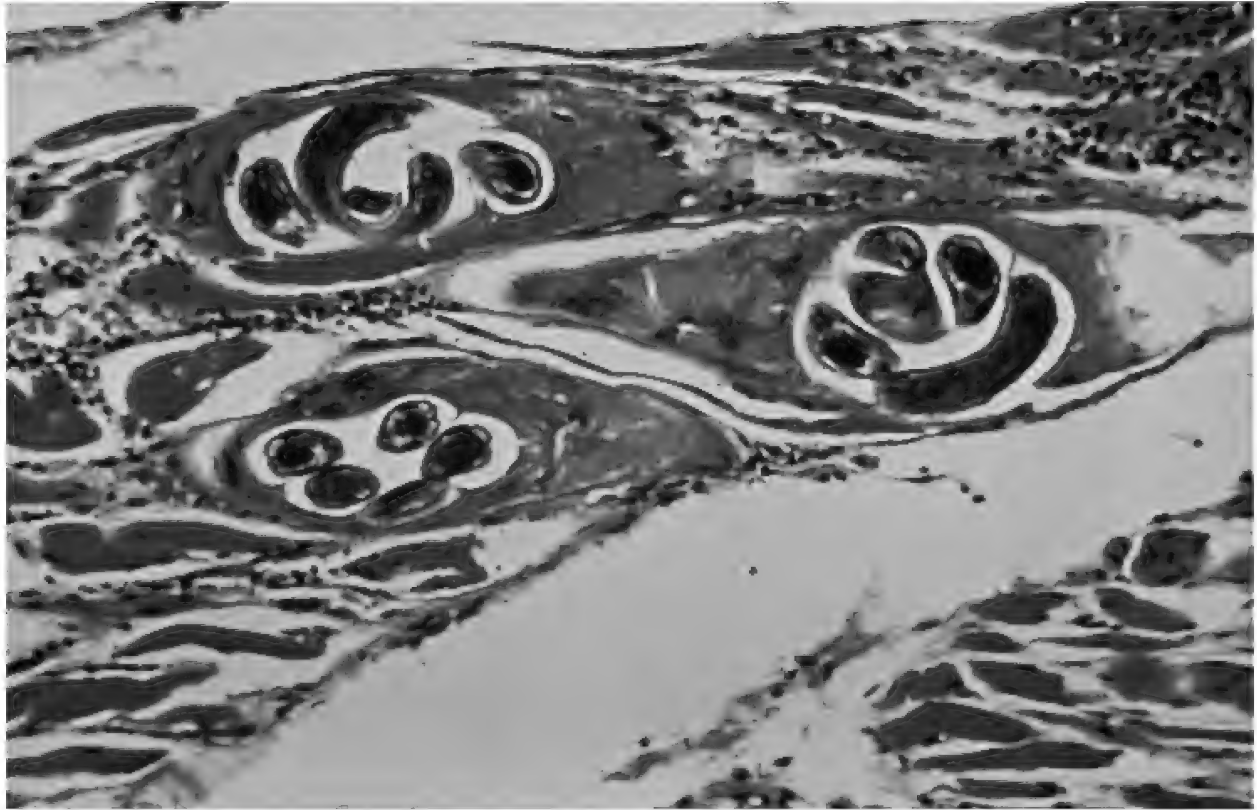


Microscopic examination of a stool specimen reveals the presence of characteristic larvae. (Source: Centers for Disease Control and Prevention, Atlanta, GA.)

Strongyloidiasis

Organism and Physical Characteristics:	<i>Strongyloides stercoralis</i> An intestinal and tissue nematode. Unique in that it has a free-living life cycle as well as a parasitic life cycle. Also called threadworm.
Etiology and Epidemiology	Found in the southern and southwestern United States and in tropical areas worldwide. Eggs require incubation in the soil for days to weeks. Infection results from direct skin penetration of filariform larvae in soil contaminated with human feces. Eggs passed in stool can develop into larvae and then adults in the soil, producing eggs and larvae outside of the host.
Clinical Manifestations	Eosinophilia may be the only manifestation of infection. Depending on the worm burden and immunologic competence of the individual, symptomatic infections can include pneumonitis, watery diarrhea, abdominal pain, and blood in the stool. Hyperinfection syndrome, associated with immunocompromised individuals (or those on corticosteroids), is characterized by larvae that disseminate to different organs including lung, CNS, and heart. Penetration of the wall of the colon can lead to secondary bacterial infections. Autoinfection is common in those with high worm burden.
Pathogenesis	After entry, larvae undergo a lung migration. Adult worms develop in the small intestine and produce eggs. Eggs can hatch in the intestine and larvae can directly penetrate the intestine, resulting in internal autoinfection. Larvae that contaminate the perianal area can cause external autoinfection. Other larvae are passed in stool. Pathology depends on the worm burden.
Laboratory Diagnosis	Stool examination may disclose characteristic larvae, but several fresh stool specimens may need to be examined before a positive one is found. Serologic assays include enzyme-linked immunosorbent assay (ELISA).
Treatment and Prevention	Ivermectin, or a benzimidazole (thiabendazole or albendazole) is curative in most patients. Prevention involves wearing shoes, education about transmission and sanitation, and proper disposal of human waste.

A 40-year-old man presents to his primary care doctor with high fever, cough, and eosinophilia. Questioning reveals that he is an avid hunter and two months ago shot a wild boar, which he cooked and ate rare.



Encysted larvae within human muscle tissue. (Source: Centers for Disease Control, Atlanta, GA.)

Trichinosis

Organism and Physical Characteristics:	<i>Trichinella spiralis</i> Nematode (roundworm). Intestinal and tissue infections.
Etiology and Epidemiology	Transmission is through ingestion of undercooked pork, bear, seal, or deer meat in which <i>T. spiralis</i> is encysted in muscle tissue. Humans are a dead-end host.
Clinical Manifestations	<i>T. spiralis</i> causes trichinosis. The intestinal stage, which lasts 1–4 months, is characterized by GI symptoms including abdominal pain, diarrhea, nausea, and vomiting. The tissue stage occurs several weeks after GI symptoms and may include rash, fever, myalgia, conjunctival and subungual bleeding, splinter hemorrhages, periorbital edema, CNS disorders, congestive heart failure, and respiratory arrest. Symptoms in the tissue stage depend on the location and load of the migrating larvae.
Pathogenesis	Ingestion of undercooked muscle containing encysted larvae, the larvae are released from the cyst during digestion, pass to the small intestine, and burrow beneath the epithelium where they develop into adults. They reenter the gut lumen, and after mating, the female worms release live larvae. The larvae produced invade the intestine and circulate through the bloodstream, and eventually encyst in striated muscle tissue. Pathogenesis results from an eosinophilic inflammatory response, which depends on the number of migrating larvae and cysts. Calcification, which may or may not destroy the larvae, occurs within 5–6 months.
Laboratory Diagnosis	Eosinophilia and detection of larvae in striated muscle from biopsy specimens as well as serology are used for diagnosis.
Treatment and Prevention	A benzimidazole (albendazole or mebendazole) has been used to kill adult worms. No methods are available to kill encysted larvae. Corticosteroids can be used to reduce inflammation. Prevention includes reducing transmission to pigs by not feeding pigs garbage, and avoiding eating undercooked meats.

A 25-year-old African man is taken to see a pair of missionaries with the hope that they will be able to help him. He has a grossly enlarged scrotum that has become infected. He is sent to a local clinic where he is given antibiotics to treat the secondary infection. Blood is collected for microscopic examination.

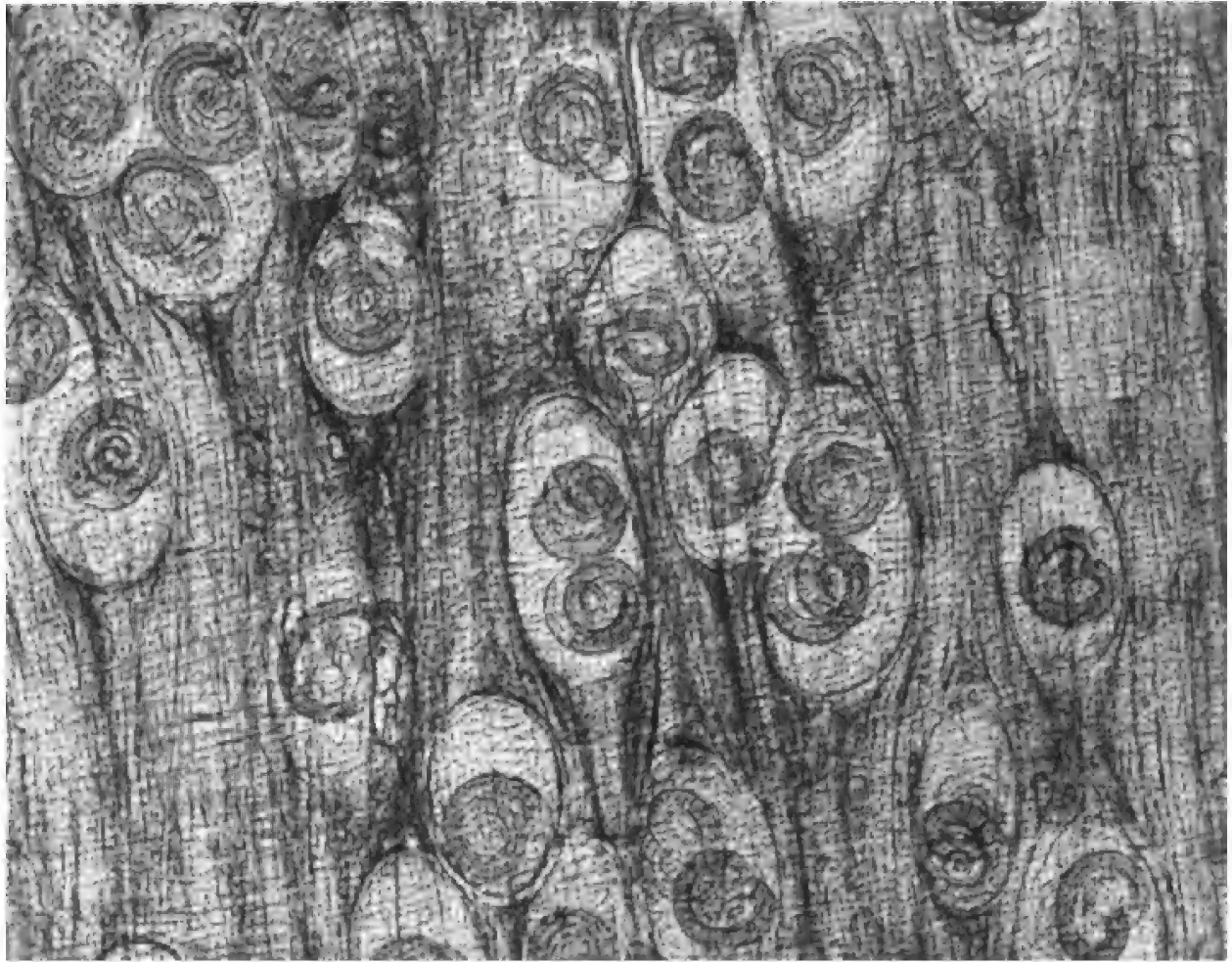


Microfilaria in a thick blood smear using Giemsa stain technique. (Source: Centers for Disease Control and Prevention, Atlanta, GA.)

Filariasis with Lymphatic Obstruction

Organism and Physical Characteristics:	<i>Wuchereria bancrofti</i> (also <i>Brugia malayi</i> and <i>B. timori</i>) Tissue-inhabiting filarial nematodes (roundworms). Transmitted by arthropod vector (mosquito).
Etiology and Epidemiology	Various genera of mosquitoes (<i>Anopheles</i> , <i>Culex</i> , <i>Aedes</i> , and <i>Mansonia</i>) can transmit <i>W bancrofti</i> . <i>W bancrofti</i> is endemic to many areas in Africa, Asia, the Western Pacific, and parts of the Caribbean and South America.
Clinical Manifestations	Most filarial infections are asymptomatic. Initial symptoms include fever, chills, myalgia, and lymphadenitis. Chronic inflammation results in obstruction of the lymphatics, which in severe cases can result in elephantiasis . Secondary bacterial infections can also occur.
Pathogenesis	Following the bite of an infected mosquito, larvae penetrate skin and migrate through the lymphatics to regional lymph nodes. After a prolonged incubation (6 months to a year), larvae develop into adults where the female releases microfilariae that migrate into the peripheral blood at night. The microfilariae are ingested by a feeding mosquito to perpetuate transmission. The adult forms can persist up to a decade. Chronic disease results from inflammation in the lymphatics causing obstruction and lymphedema. Repeated infections increase the worm burden, leading to more severe disease manifestations.
Laboratory Diagnosis	Thick-smear blood examination should be performed with samples collected between 10 pm and 4 am. Circulating filarial antigen (CFA) assays have been developed for diagnosis of <i>W bancrofti</i> infections only; no assays have been developed yet for diagnosis of <i>Brugia</i> species. infections).
Treatment and Prevention	Diethylcarbamazine (DEC) is used to kill adults and microfilariae. Surgery may be necessary to relieve obstructions. Prevention involves mosquito control, and use of personal exposure barriers and repellents. Recently, community-wide treatment has been used to reduce transmission in high-risk areas.

A 30-year-old West African man presents to a clinic with multiple fibrous subcutaneous nodules on his lower torso, pelvis, and lower extremities. He complains that he cannot see very well and his eyes are sensitive to sunlight. A slit-lamp examination of the anterior chamber of the man's eyes reveals the presence of motile microfilariae. A skin biopsy is obtained and examined microscopically.



Examination of skin biopsy reveals the presence of microfilariae. (Source: Centers for Disease Control and Prevention, Atlanta, GA.)

Onchocerciasis (River Blindness)

Organism and Physical Characteristics:	<i>Onchocerca volvulus</i> A filarial nematode (roundworm). Transmitted by arthropod vector.
Etiology and Epidemiology	The vectors of transmission are black flies of the genus <i>Simulium</i> that breed in fast-flowing streams and rivers. Endemic areas include equatorial Africa, Yemen, and Central and South America.
Clinical Manifestations	Causative agent of river blindness. Symptoms include skin rash, itching, loss of elasticity in subcutaneous tissue (leading to large skin folds), and partial to total blindness.
Pathogenesis	When larvae enter the bite wound, they migrate to subcutaneous tissue where they become encapsulated with host tissue to form a nodule (onchocercoma), and where they develop into adults. Adult worms mate, and the female releases microfilariae that migrate through the subcutaneous tissue and skin, where they can be ingested by biting black flies, perpetuating spread. Pathogenesis results from hypersensitivity to parasite antigens and to inflammation associated with migrating larvae. The presence of microfilariae in ocular structures leads to photophobia and inflammation of the cornea, iris, ciliary body, retina, choroids, and optic nerve. Visual loss develops over many years from an accumulation of microfilariae in the vitreous humor.
Laboratory Diagnosis	Microfilariae can be seen in skin biopsies and by slit-lamp examination of the anterior chamber of an involved eye.
Treatment and Prevention	Treatment involves surgical removal of adult dermal nodules in combination with ivermectin (to kill microfilariae). Prevention involves infection control measures. Prophylactic ivermectin treatment in endemic areas can reduce the microfilarial load.

A 4-year-old set of male twins receive a new puppy for Christmas. The twins' mother is a microbiology professor at a local medical school with expertise in parasitology. Because the twins have been known, on occasion, to eat dirt while playing outside, the mother immediately takes the puppy to the veterinarian for deworming where examination of a rectal swab reveals characteristic eggs.

Toxocariasis (Visceral Larva Migrans)

Organism and Physical Characteristics:	<i>Toxocara canis</i> and <i>Toxocara cati</i> Nematode (roundworm). Tissue manifestations. Visceral larva migrans.
Etiology and Epidemiology	Humans are dead-end hosts. Dogs (<i>T. canis</i>) and cats (<i>T. cati</i>) are definitive hosts. Dogs and cats pass <i>Toxocara</i> eggs in their stool. Humans (typically children 1–4 years of age with a history of pica) become infected by ingesting eggs.
Clinical Manifestations	Many individuals are asymptomatic. Depending on the location of larvae, some may experience abdominal pain, rash, fever, hepatomegaly, retinal involvement leading to blindness, or cardiac, respiratory, or CNS manifestations.
Pathogenesis	Once eggs are ingested, larvae develop, which migrate to multiple organs including lungs, liver, kidney, heart, eyes, muscle, and CNS. The larvae encyst as second-stage larvae. Migrating larvae produce tracts with hemorrhagic necrosis and eosinophilic and lymphocytic infiltration. Granulomas may develop around disintegrating larvae. Pathogenesis results from the severity of the inflammation and the location and load of the dead larvae.
Laboratory Diagnosis	Hypereosinophilia and hypergammaglobulinemia associated with elevated titers of isohemagglutinin to the A and B blood group antigens are presumptive evidence of infection. Diagnosis involves serologic testing, examination of tissue biopsies for larvae, and clinical signs and symptoms. Pets can be examined for eggs in stool.
Treatment and Prevention	A benzimidazole (mebendazole or albendazole) is used for treatment. Prevention involves deworming pets and pet hygiene.

Cestodes



Taenia solium
Taenia saginata
Diphyllobothrium latum
Echinococcus granulosus
Hymenolepis nana

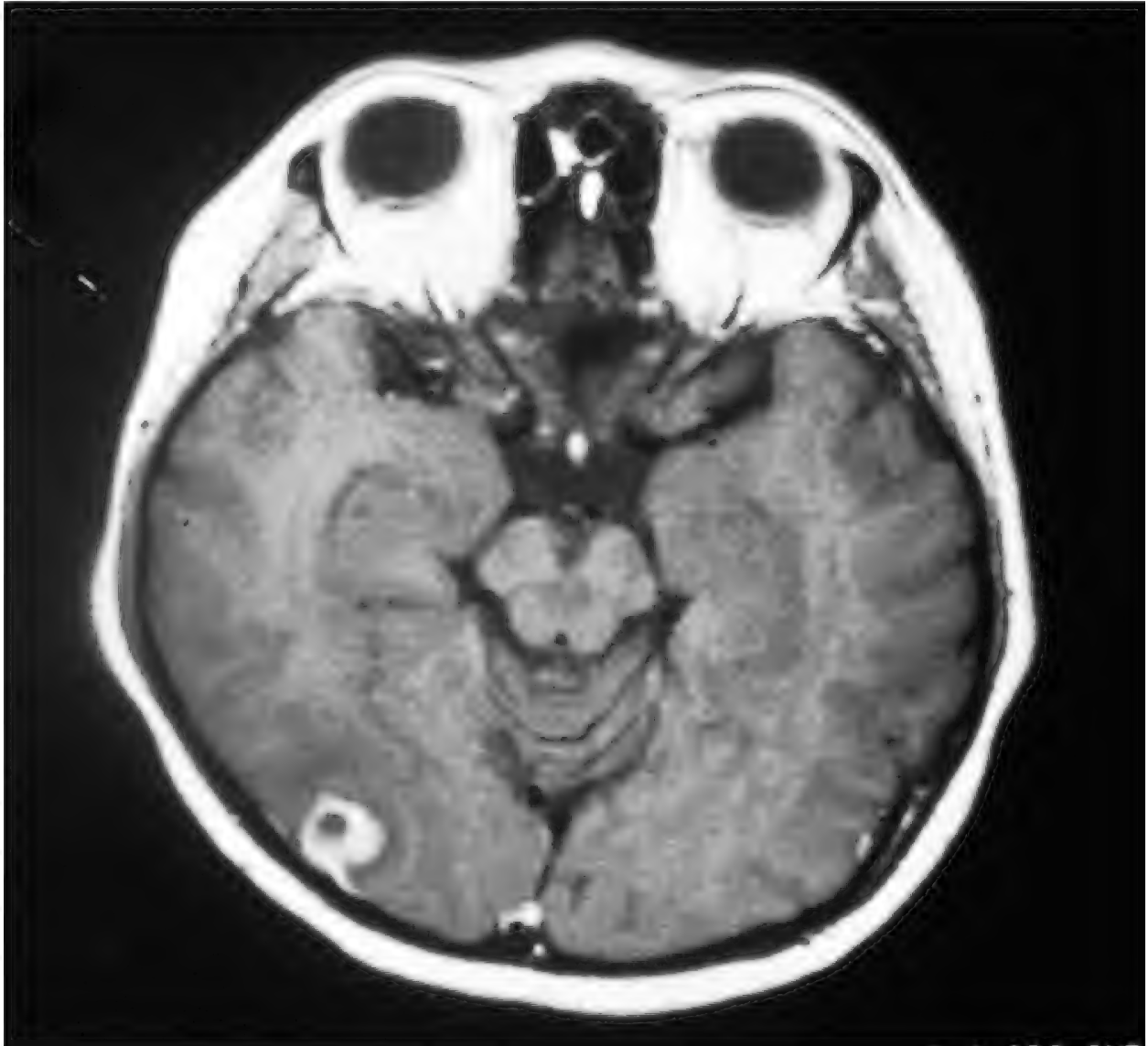
KEY CONCEPTS

- Cestodes are segmented flatworms with three types of body parts: The **scolex**, or “head,” which serves as the holdfast organ; the **neck**, from which partially segmented young proglottids develop; and the **strobila**, or body.
- The strobila consists of one or more hermaphroditic **proglottids**.
 - ▶ There is no mouth and no trace of an alimentary system. Instead, glucose and other predigested nutrients are absorbed directly from the host gut through submicroscopic hair-like extensions (**microtriches**), which interdigitate with the host’s microvilli.

PROPERTIES OF CESTODES

	<i>T. solium</i>	<i>T. saginata</i>	<i>D. latum</i>	<i>E. granulosus</i>	<i>H. nana</i>
Common Name	Pork tapeworm	Beef tapeworm	Broad fish tapeworm		Dwarf tapeworm
Definitive Host	Human	Human	Human	Canines	Human
Intermediate Hosts	Pigs	Cattle	Crustaceans, then fish	Sheep or human	None
Adult Size	5 m	10 m	13 m	5 cm	2–4 cm
Transmission	Ingestion of under-cooked pork	Ingestion of undercooked beef	Ingestion of undercooked fish	Canine fecal to human oral	Fecal-oral

A 28-year-old woman with meningoencephalitis is taken to the Emergency Department. Magnetic resonance imaging reveals the presence of calcified cysticerci in the brain. The woman's mother says that the family raises pigs and eats pork 3–4 times per week.

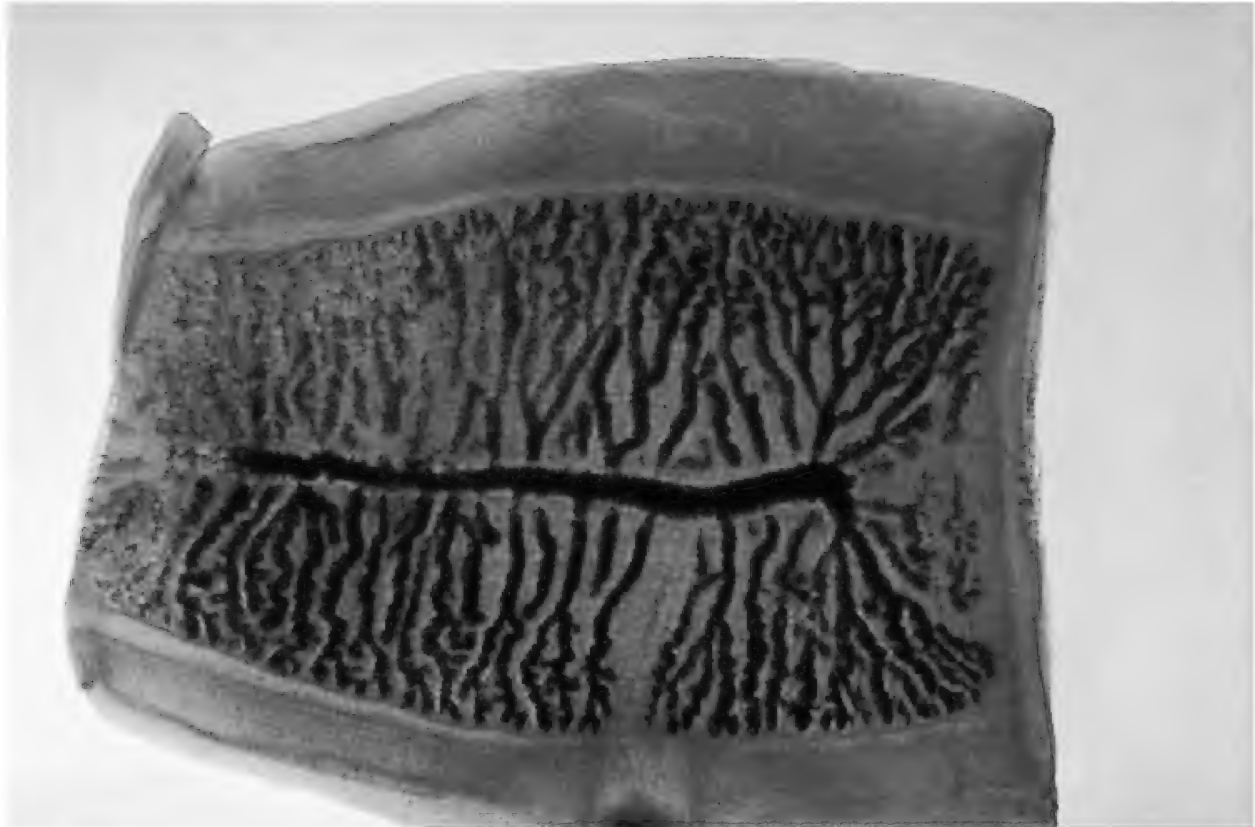


A single cysticercus seen in a magnetic resonance imaging scan of the brain. (Source: Centers for Disease Control and Prevention, Atlanta, GA.)

Cysticercosis with Neurologic Involvement (Neurocysticercosis)

Organism and Physical Characteristics:	<i>Taenia solium</i> Cestode (segmented flatworm), pork tapeworm. Strobila contains one or more hermaphroditic proglottids.
Etiology and Epidemiology	Humans are the definitive host and pigs are the intermediate host. Eggs are ingested by pigs, and the larvae burrow through the intestinal wall, enter the bloodstream, and spread to skeletal muscle. Human infection results from ingestion of undercooked pork infected with encysted larvae. Adult tapeworms develop in the intestine and shed proglottids containing eggs into the stool. Fecal-oral transmission of eggs—either from someone else, such as a family member or other contact, who is harboring the adult tapeworm or by autoinfection—results in cysticercosis.
Clinical Manifestations	Adult tapeworm infections generally yield mild gastrointestinal symptoms or are asymptomatic. Cysticercosis is more serious and leads to the formation of cysticerci in different tissues in humans including the eye, brain, spinal cord, muscle, and lungs. The symptoms vary depending on the location of the cysticerci, but neurocysticercosis can include meningoencephalitis, seizures, and other neurologic manifestations.
Pathogenesis	Adult tapeworms remain attached to the small intestine by way of the scolex and can grow 2–7 m in length. If untreated, they can survive for decades. In cysticercosis, eggs are directly ingested and hatch into oncospheres in the intestine that then migrate to tissues throughout the body.
Laboratory Diagnosis	Demonstration of proglottids with 5–13 uterine branches or ova in feces or the perianal region is diagnostic. Because cysticerci often calcify, they can be seen by radiographic imaging such as X-ray, computed tomography (CT), or magnetic resonance imaging (MRI).
Treatment and Prevention	Adult tapeworm infections are treated with praziquantel. Cysticercosis is treated by surgical excision and/or an antiparasitic drug (praziquantel or albendazole) with anti-inflammatory drugs. Neurocysticercosis may also require addition of antiseizure medications. Prevention involves avoidance of undercooked pork, good hand hygiene, and appropriate sanitary measures designed to prevent fecal-oral spread.

A 30-year-old man experiencing mild gastrointestinal symptoms is seen by his primary care doctor and asked to provide a stool sample for evaluation. An examination of the stool indicates the presence of proglottids with an intricate pattern of 20 uterine branches. Upon further questioning, the man admits to regularly eating raw ground beef. He is started on a course of praziquantel.



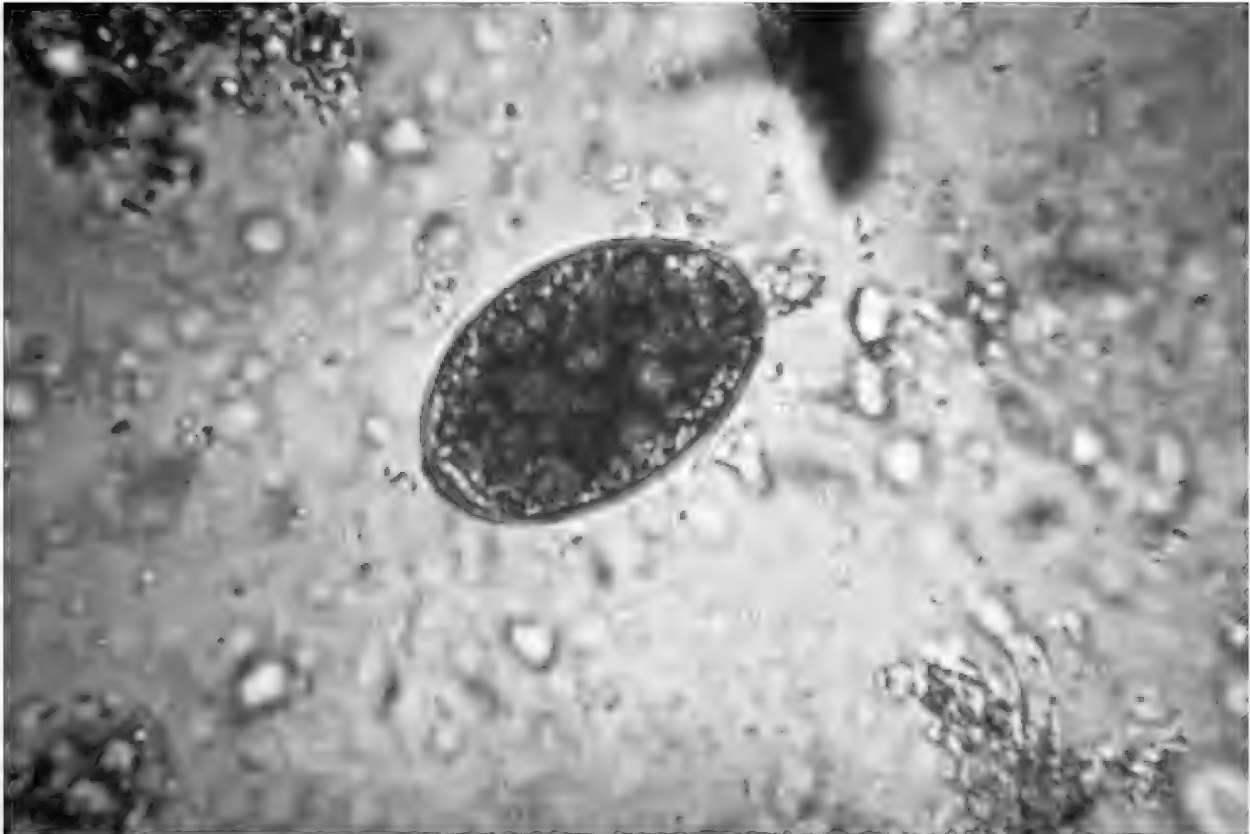
Characteristic gravid proglottid showing 15–30 branches on a side. (Source: Centers for Disease Control and Prevention, Atlanta, GA.)

Taeniasis (Beef Tapeworm Infection)

Organism and Physical Characteristics:	<i>Taenia saginata</i> Cestode (segmented flatworm), beef tapeworm. Strobila contains one or more hermaphroditic proglottids.
Etiology and Epidemiology	Humans are the definitive host; cattle are the intermediate host. Human infection results from ingestion of raw or undercooked beef. Cysticercosis does not occur with <i>T saginata</i> .
Clinical Manifestations	Adult tapeworm infections cause mild gastrointestinal symptoms or are asymptomatic.
Pathogenesis	Adult tapeworms remain attached to the intestine by way of the scolex and can grow up to 10 m in length.
Laboratory Diagnosis	Demonstration of proglottids with 15–30 uterine branches or ova in feces or the perianal region is diagnostic.
Treatment and Prevention	Praziquantel is often used for treatment. Prevention involves avoiding undercooked beef and proper disposal of human waste to prevent infection in cattle.
Notes	

A 20-year-old college student spent a summer abroad in Norway. While there,

she was introduced to the joys of eating raw fish. She consumed several meals of raw freshwater fish during her stay. About 7 months later, she presents to the student health clinic complaining of weight loss and is found to be anemic with below-normal levels of vitamin B12. A stool sample is collected for microscopic examination. Proglottids that are wider than they are long are seen, as well as a few elongated eggs with an operculum. She is started on a course of praziquantel.



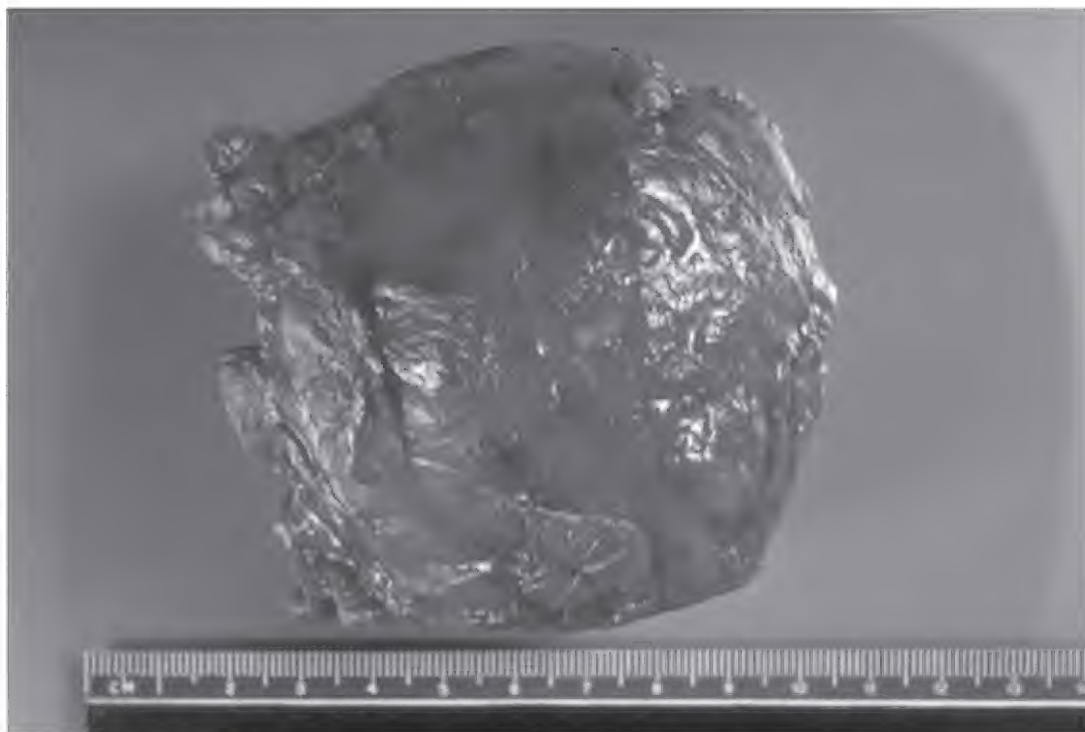
Microscopic examination reveals the presence of characteristic eggs. (Source: Centers for Disease Control and Prevention, Atlanta, GA)

Diphyllobothriasis Associated with Anemia

Organism and Physical Characteristics:	<i>Diphyllobothrium latum</i> Cestode (segmented flatworm), broad fish tapeworm. Strobila contains one or more hermaphroditic proglottids.
Etiology and Epidemiology	Humans are the definitive host. <i>D latum</i> has two sequential intermediate hosts: the freshwater copepod (<i>Cyclops</i>) and freshwater fish. Infection occurs following ingestion of undercooked, pickled, or raw freshwater fish.
Clinical Manifestations	Most infections are asymptomatic; however, competition for vitamin B12 leads to a B12 deficiency, which can result in megaloblastic anemia and various neurologic symptoms.
Pathogenesis	Adult tapeworms remain attached to the intestine by way of the scolex and can grow up to 13 m in length.
Laboratory Diagnosis	The eggs of <i>D latum</i> are elongated and have a lid-like operculum. The proglottids are wider than they are long, with a rosette pattern of uterine branches.
Treatment and Prevention	Praziquantel is used for treatment. Prevention involves avoidance of undercooked fish and measures to prevent human waste contamination of freshwater lakes.

Notes

A 60-year-old immigrant from Argentina experiencing upper quadrant pain, nausea, and vomiting is taken to the emergency room by his wife. A CT scan reveals a large mass in his liver. History reveals that the man raised sheep in Argentina. A surgical consult is arranged to remove the cyst.



Cyst in liver that was surgically removed. (Source: Centers for Disease Control and Prevention, Atlanta, GA)

Echinococcosis (Hydatid Cyst Disease)

Organism and Physical Characteristics:	<i>Echinococcus granulosus</i> Cestode (segmented flatworm). Very small with a scolex and only three proglottids.
Etiology and Epidemiology	Canines are the definitive host and sheep are intermediate hosts. Dogs become infected by eating sheep viscera. Infection in humans results from ingestion of eggs in food or water contaminated with dog feces. Humans are considered inadvertent intermediate hosts, and cysts can develop in various organs. Adult worms do not develop in humans.
Clinical Manifestations	<i>E. granulosus</i> causes hydatid cyst disease. This infection can be asymptomatic or can exhibit a variety of lung, brain, or liver manifestations depending on the site of the cyst.
Pathogenesis	After ingestion of eggs, embryos develop and invade intestinal cells to enter the bloodstream. Larvae develop within tissues and form a fluid-filled cyst (hydatid cyst) containing brood capsules filled with protoscolices. The hydatid cysts can be as large as 20 cm in diameter, resulting in the observed pathogenesis when found in various organs. Rupture of the cyst results in dissemination of infectious protoscolices and can induce an anaphylactic reaction.
Laboratory Diagnosis	Diagnosis is by serologic testing or by X-ray or CT to detect hydatid cysts.
Treatment and Prevention	Treatment involves careful surgical removal of the hydatid cyst and a course of albendazole. Prevention involves de-worming of dogs, not feeding dogs sheep viscera, and hygienic practices to prevent contamination of food and water with dog feces.

A 10-year-old girl living in a rural area outside of Atlanta has experienced diarrhea, accompanied by abdominal pain and vomiting for the past several weeks. A stool sample is collected and sent to the laboratory for microscopic examination. Distinctive eggs containing a six-hooked embryo are observed. A course of praziquantel is begun.



Microscopic examination reveals the presence of distinctive eggs. (Source: Centers for Disease Control and Prevention, Atlanta, GA.)

Cestode-Induced Diarrhea

Organism and Physical Characteristics:	<i>Hymenolepis nana</i> Cestode (segmented flatworm), dwarf tapeworm. Smallest of the adult tapeworms. Entire life cycle is in humans.
Etiology and Epidemiology	Humans are the definitive host and there are no required intermediate hosts. Transmission is fecal-oral. Especially prevalent in children. <i>H nana</i> is one of the most common tapeworm infections, especially in the southeastern United States.
Clinical Manifestations	Infections are generally asymptomatic with small worm burdens; however, more gastrointestinal symptoms develop as the worm burden increases.
Pathogenesis	Eggs are directly infectious. Once ingested, larvae develop that attach to the intestine. Adult worms are small, 2–5 cm in length, and produce eggs that are passed in stool. Autoinfection of the host can occur, resulting in a greater worm burden, which can be hundreds of worms.
Laboratory Diagnosis	<i>H nana</i> eggs (with a six-hooked embryo) in stool are diagnostic.
Treatment and Prevention	Treatment typically involves praziquantel. Prevention is best accomplished through good hygiene and sanitary measures that eliminate fecal-oral transmission.
Notes	

Trematodes






Schistosoma mansoni
Schistosoma japonicum
Schistosoma haematobium

KEY CONCEPTS

- Trematodes are soft-bodied syncytial worms commonly called flukes. Important parasites of humans include: **Schistosoma mansoni**, **S japonicum**, **S haematobium**, **Clonorchis sinensis**, **Fasciola hepatica**, **Fasciolopsis buski**, and **Paragonimus westermani**.
- Trematodes undergo a complex asexual reproductive phase through several distinct generations of larval stages in an intermediate host, usually a snail.
- The primary host where the flukes sexually reproduce is a vertebrate. In the human host, adult flukes can inhabit the portal blood vessels, intestine, liver, or lungs.
- One of the most common causes of infectious disease mortality worldwide.

PROPERTIES OF SCHISTOSOMES*

	<i>S. mansoni</i>	<i>S. japonicum</i>	<i>S. haematobium</i>
World Distribution	Africa, South America, Caribbean, Middle East, West Indies, Puerto Rico	Far East, China, Japan, Indonesia, Philippines	Africa, Middle East, South Asia
Egg Characteristics	Sharp lateral spine  Eggs are large and rounded with a slightly tapered anterior end and prominent lateral spine at posterior end: 114–180 μ long and 45–70 μ wide	Inconspicuous spine  Eggs are large and more rounded: 70–100 μ long and 55–64 μ wide	Terminal spine  Eggs are large and more tapered appearing with characteristic terminal spine: 110–170 μ long and 40–70 μ wide
Adult Location	Mesenteric veins in colon	Mesenteric veins in small intestine and colon	Veins around the bladder and pelvic organs
Egg Transmission	Feces	Feces	Urine

Source: Centers for Disease Control and Prevention, Atlanta, GA.
*Two other species, *S. mekongi* and *S. intercalatum* are found focally in Southeast Asia and central West Africa, respectively.

A 15-year-old boy develops a transient, pruritic papular rash after swimming in a freshwater pond while vacationing in Puerto Rico. One month later, he develops a fever and experiences malaise, abdominal pain, nausea, and diarrhea. A stool sample is collected and sent to the laboratory for microscopic evaluation. The lab report returns positive for eggs, described as having a prominent lateral spine. A course of praziquantel is started.

Schistosomiasis

Organism and Physical Characteristics:	<i>Schistosoma</i> species Trematode—nonsegmented flatworm or fluke. Three common species of human schistosomes: <i>S. mansoni</i> , <i>S. japonicum</i> , and <i>S. haematobium</i> .
Etiology and Epidemiology	Snails are intermediate hosts. Humans are definitive hosts. Cercariae penetrate the skin of humans, become adult flukes, and lay eggs that are shed in urine (<i>S. haematobium</i>) or stool (<i>S. mansoni</i> and <i>S. japonicum</i>). Endemic areas include Africa, South America, Middle East, West Indies, and Puerto Rico (<i>S. mansoni</i>); China, Japan, and Philippines (<i>S. japonicum</i>); Africa, Middle East, and South Asia (<i>S. haematobium</i>). Swimmer's itch is a reaction that results from the dermal penetration of cercariae from avian and mammalian species of <i>Schistosoma</i> .
Clinical Manifestations	A transient, pruritic papular rash may occur shortly after skin penetration by cercariae. Acute schistosomiasis (Katayama fever) may occur weeks after the initial infection, especially in infections caused by <i>S. mansoni</i> and <i>S. japonicum</i> ; manifestations include fever, chills, cough, abdominal pain, diarrhea, hepatosplenomegaly, and eosinophilia. Chronic disease depends on the location of the adult worms in the human host. <i>S. mansoni</i> and <i>S. japonicum</i> cause abdominal pain, bloody diarrhea, and hepatosplenomegaly. <i>S. haematobium</i> causes hematuria, dysuria, and obstruction and is associated with bladder carcinoma .
Pathogenesis	After skin penetration, the organism enters the bloodstream and migrates through the lungs. Each of the three-major human schistosome parasites lives in some part of the venous plexus that drains the intestines or bladder depending on the species (mesenteric veins of colon for <i>S. mansoni</i> ; mesenteric veins of small bowel and colon for <i>S. japonicum</i> ; veins around the bladder and pelvic organs for <i>S. haematobium</i>) and produces eggs. Pathogenesis results from the immune response to the eggs, causing abscesses, fibrosis, granulomas, and scarring. The eggs produce hydrolytic enzymes that destroy tissue and promote shedding.
Laboratory Diagnosis	Characteristic eggs present in stool or urine.
Treatment and Prevention	Praziquantel can be used for treatment. Prevention involves proper waste management, avoiding swimming in freshwater in endemic areas, and eradication of snail populations.

SKIN AND SOFT-TISSUE INFECTIONS

BACTERIAL AGENTS

Organism	Clinical Manifestation	Organism	Clinical Manifestation
<i>Treponema pallidum</i>	Chancre, maculopapular rash	<i>Rickettsia rickettsii</i>	Rash
<i>Borrelia burgdorferi</i>	Erythema migrans	<i>Rickettsia prowazekii</i>	Rash
<i>Francisella tularensis</i>	Skin ulcer	<i>Clostridium perfringens</i>	Myonecrosis, gas gangrene, cellulitis
<i>Pasteurella multocida</i>	Cellulitis, abscess	<i>Haemophilus influenzae</i>	Cellulitis
<i>Staphylococcus aureus</i>	Cellulitis, abscesses, folliculitis, impetigo	<i>Pseudomonas aeruginosa</i>	Folliculitis
<i>Streptococcus pyogenes</i>	Folliculitis, impetigo, erysipelas, necrotizing fasciitis	<i>Bacillus anthracis</i>	Cutaneous anthrax, eschar
<i>Mycobacterium leprae</i>	Leprosy	<i>Nocardia spp.</i>	Cellulitis, nodules, subcutaneous abscesses, lymphangitis

VIRAL AGENTS

DNA Viruses	Clinical Manifestation	RNA Viruses	Clinical Manifestation
Herpes simplex Types 1 and 2	Gingivostomatitis, Herpes genitalis	Measles	Maculopapular rash with red to reddish-brown lesions that typically appear first on face and then on trunk and extremities
Varicella zoster	Chicken pox (vesicles that appear in varying stages from newly formed to healing and forming scabs), shingles	Rubella	Maculopapular rash—a fine pink rash that typically starts on the face and then spreads downwards to trunk and arms and legs with disappearance of rash in same sequence
HHV-6	Exanthem subitum or roseola (macules)	Dengue	1-2 days after symptoms begin a rash (flushed skin) appears. Later in the course of infection, the rash becomes measles-like
HPV	Common warts, anogenital warts	Chikungunya	Maculopapular rash appearing 2-5 days after onset of symptoms
Molluscum contagiosum	Fleshy nodules		
Variola	Smallpox (papules, vesicles, pustules)—lesions all appear to be uniform and at the same stage		
Parovirus B19	Erythema infectiosum (maculopapular rash), also known as "slapped cheek syndrome" and "fifth disease"		

SKIN AND SOFT-TISSUE INFECTIONS

FUNGAL AGENTS

Organism	Clinical Manifestation	Organism	Clinical Manifestation
<i>Malassezia furfur</i>	Pityriasis versicolor	<i>Exophiala werneckii</i>	Tinea nigra
<i>Piedraia hortae</i>	Black piedra (usually affects scalp hair)	Dermatophytes (<i>Microsporum</i> , <i>Trichophyton</i> , <i>Epidermophyton</i>)	Tineas (ringworm, onychomycosis)
<i>Trichosporon asahii</i>	White piedra (usually affects eyebrows, eyelashes, facial hair, axillary hair, and/or pubic hair)	<i>Sporothrix schenckii</i>	Sporotrichosis ("Rose gardener's disease")
<i>Candida</i> species.	Diaper rash, vaginal yeast infection, oral thrush		

PARASITIC AGENTS

Organism	Clinical Manifestation	Organism	Clinical Manifestation
<i>Leishmania brasiliensis</i>	Mucocutaneous leishmaniasis	<i>Leishmania tropica</i> , <i>Leishmania mexicana</i>	Cutaneous ulcers
<i>Schistosoma mansoni</i>	Dermatitis	<i>Ancylostoma duodenale</i> , <i>Necator americanus</i>	Rash
<i>Trypanosoma cruzi</i>	Rash	<i>Trichinella spiralis</i>	Rash
<i>Onchocerca volvulus</i>	Rash		

RESPIRATORY INVOLVEMENT

BACTERIAL AGENTS

Organism	Clinical Manifestation	Organism	Clinical Manifestation
<i>Mycoplasma pneumoniae</i>	Atypical pneumonia	<i>Legionella pneumophila</i>	Atypical pneumonia
<i>Chlamydophila pneumoniae</i>	Atypical pneumonia	<i>Chlamydophila psittaci</i>	Psittacosis
<i>Chlamydia trachomatis</i>	Infant pneumonia	<i>Mycobacterium tuberculosis</i>	Tuberculosis
<i>Klebsiella pneumoniae</i>	Pneumonia, necrotizing pneumonia	<i>Streptococcus pneumoniae</i>	Pneumonia, otitis media
<i>Haemophilus influenzae</i>	Pneumonia, otitis media, epiglottitis, pharyngitis	<i>Neisseria gonorrhoeae</i>	Pharyngitis
<i>Corynebacterium diphtheriae</i>	Pharyngitis	<i>Streptococcus pyogenes</i>	Pharyngitis
<i>Bordetella pertussis</i>	Whooping cough, bronchitis	<i>Bacillus anthracis</i>	Inhalational anthrax
<i>Staphylococcus aureus</i>	Pneumonia	<i>Pseudomonas aeruginosa</i>	Pneumonia, especially in CF patients
<i>Yersinia pestis</i>	Pneumonic plague	<i>Francisella tularensis</i>	Pneumonic tularemia
<i>Nocardia spp.</i>	Pneumonia, lung nodules, lung mass with or without cavitation		

RESPIRATORY INVOLVEMENT

VIRAL AGENTS

DNA Viruses	Clinical Manifestation	RNA Viruses	Clinical Manifestation
Parvovirus B19	Erythema infectiosum	Rhinovirus	Common cold
Adenovirus	Pharyngitis, pneumonia, ARDS, common cold	Coxsackievirus A/B and echovirus	Herpangina, pleurodynia, common cold
Varicella-zoster virus	Chickenpox, shingles, pneumonia	Parainfluenza virus	Croup, bronchiolitis, pneumonia, common cold
CMV	Pharyngitis, pneumonia	Measles virus	Measles, pneumonia
EBV	Pharyngitis, infectious mononucleosis	Mumps virus	Mumps, parotitis, orchitis
Variola virus	Smallpox	RSV	Bronchiolitis, pneumonia
		Human metapneumovirus	Bronchiolitis, pneumonia
		Influenza A/B virus	Influenza, pneumonia
		Coronavirus	Common cold, SARS, MERS
		Hantavirus	Hantavirus pulmonary syndrome
		Rubella virus	Rubella, congenital rubella syndrome

RESPIRATORY INVOLVEMENT

FUNGAL AGENTS

Organism	Clinical Manifestation	Organism	Clinical Manifestation
<i>Candida</i> species	Pulmonary nodules (immunocompromised host)	<i>Fusarium</i> species	Pneumonia, immunocompromised
<i>Histoplasma capsulatum</i>	Pneumonia	<i>Pneumocystis jiroveci</i>	Pneumonia, immunocompromised
<i>Blastomyces dermatitidis</i>	Pneumonia	<i>Cryptococcus neoformans</i> , <i>Cryptococcus gattii</i>	Pneumonia, immunocompromised
<i>Coccidioides immitis</i>	Pneumonia	<i>Scedosporium</i> species	Pneumonia, immunocompromised
<i>Paracoccidioides brasiliensis</i>	Pneumonia	Zygomycoses (<i>Rhizopus</i> , <i>Mucor</i>) species	Pneumonia, immunocompromised
<i>Aspergillus</i> species	Pneumonia, immunocompromised		

RESPIRATORY INVOLVEMENT

PARASITIC AGENTS

Organism	Clinical Manifestation	Organism	Clinical Manifestation
<i>Ascaris lumbricoides</i>	Pneumonitis	<i>Strongyloides stercoralis</i>	Pneumonitis
<i>Ancylostoma duodenale</i>	Pneumonitis	<i>Necator americanus</i>	Pneumonitis

GASTROINTESTINAL INFECTIONS

BACTERIAL AGENTS

Organism	Clinical Manifestation	Organism	Clinical Manifestation
<i>Escherichia coli</i> (ETEC)	Watery diarrhea	<i>Salmonella enterica</i>	Dysentery
<i>Escherichia coli</i> (EHEC)	Hemorrhagic colitis	<i>Shigella species</i>	Dysentery
<i>Escherichia coli</i> (EPEC)	Watery diarrhea (infants)	<i>Yersinia enterocolitica</i>	Dysentery
<i>Escherichia coli</i> (EAEC)	Watery diarrhea (infants)	<i>Campylobacter jejuni</i>	Watery diarrhea, dysentery
<i>Escherichia coli</i> (EIEC)	Dysentery	<i>Vibrio cholerae</i>	Watery diarrhea
<i>Clostridium perfringens</i>	Watery diarrhea	<i>Clostridium difficile</i>	Diarrhea, pseudomembranous colitis, toxic megacolon
<i>Helicobacter pylori</i>	Gastric ulcers, gastritis	<i>Vibrio parahaemolyticus</i>	Watery diarrhea

VIRAL AGENTS

DNA Viruses	Clinical Manifestation	RNA Viruses	Clinical Manifestation
Enteric adenoviruses	Acute gastroenteritis	Rotavirus	Acute gastroenteritis
		Norovirus	Acute gastroenteritis
		Astrovirus	Acute gastroenteritis

GASTROINTESTINAL INFECTIONS

FUNGAL AGENTS

Organism	Clinical Manifestation
<i>Candida albicans</i>	Oral thrush, esophageal candidiasis or esophagitis in immunocompromised or HIV/AIDS patients

PARASITIC AGENTS

Organism	Clinical Manifestation	Organism	Clinical Manifestation
<i>Giardia lamblia</i>	Watery diarrhea	<i>Cryptosporidium parvum</i>	Watery diarrhea
<i>Entamoeba histolytica</i>	Bloody diarrhea, dysentery	<i>Balantidium coli</i>	Bloody diarrhea
<i>Ascaris lumbricoides</i>	Intestinal obstruction	<i>Taenia solium, Taenia saginata, Diphylobothrium latum, Hymenolepis nana</i>	Mild GI symptoms
<i>Enterobius vermicularis</i>	Perianal pruritus	<i>Trichuris trichiura</i>	Bloody diarrhea
<i>Strongyloides stercoralis</i>	Bloody diarrhea	<i>Schistosoma</i> species	Bloody diarrhea
<i>Ancylostoma duodenale</i>	Chronic anemia	<i>Necator americanus</i>	Anemia

EYE INFECTIONS

BACTERIAL AGENTS

Organism	Clinical Manifestation	Organism	Clinical Manifestation
<i>Leptospira interrogans</i>	Iritis	<i>Haemophilus influenzae</i>	Conjunctivitis
<i>Bacillus cereus</i>	Traumatic eye infections	<i>Neisseria gonorrhoeae</i>	Conjunctivitis
<i>Staphylococcus aureus</i>	Stye (blepharitis), conjunctivitis	<i>Chlamydia trachomatis</i>	Conjunctivitis, keratoconjunctivitis (trachoma)
<i>Francisella tularensis</i>	Conjunctivitis	<i>Treponema pallidum</i>	Uveitis, retinitis, chorioretinitis, vitritis, panuveitis

VIRAL AGENTS

DNA Viruses	Clinical Manifestations	RNA Viruses	Clinical Manifestations
Herpes simplex Types 1 and 2	Keratoconjunctivitis	Measles	Conjunctivitis
Varicella-zoster	Keratoconjunctivitis	Rubella	Cataracts (infection in utero)
Cytomegalovirus	Chorioretinitis	Coxsackie A	Hemorrhagic conjunctivitis
Adenovirus	Keratoconjunctivitis, pharyngoconjunctival fever		

EYE INFECTIONS

FUNGAL AGENTS

Organism	Clinical Manifestations
<i>Candida</i> species	Endophthalmitis
<i>Scedosporium</i> species	Endophthalmitis
<i>Fusarium</i> species	Endophthalmitis, keratitis

PARASITIC AGENTS

Organism	Clinical Manifestations
<i>Trypanosoma cruzi</i>	Conjunctivitis
<i>Trichinella spiralis</i>	Hemorrhagic conjunctivitis
<i>Onchocerca volvulus</i>	Keratoconjunctivitis
<i>Toxocara canis</i>	Chorioretinitis
<i>Toxoplasma gondii</i>	Chorioretinitis

CNS INFECTIONS

BACTERIAL AGENTS

Organism	Clinical Manifestations	Organism	Clinical Manifestations
<i>E coli</i>	Neonatal meningitis	<i>Chlamydophila psittaci</i>	Encephalitis
<i>Streptococcus agalactiae</i>	Neonatal meningitis	<i>Rickettsia rickettsii</i>	Encephalitis
<i>Listeria monocytogenes</i>	Neonatal meningitis, meningitis (children/adults)	<i>Rickettsia prowazekii</i>	Meningoencephalitis
<i>Haemophilus influenzae</i>	Meningitis (children/adults)	<i>Borrelia burgdorferi</i>	Meningoencephalitis
<i>Neisseria meningitidis</i>	Meningitis (children/adults)	<i>Treponema pallidum</i>	Neurosyphilis
<i>Streptococcus pneumoniae</i>	Meningitis (children/adults)	<i>Mycobacterium tuberculosis</i>	Tuberculous meningitis
<i>Staphylococcus aureus</i>	Meningitis (children/adults), brain abscesses	<i>Nocardia</i> species	Brain abscess

FUNGAL AGENTS

Organism	Clinical Manifestations
<i>Cryptococcus neoformans</i> and <i>C. gattii</i>	Meningitis in immunocompromised or AIDS patients
Zygomycoses (eg, <i>Rhizopus</i>) species	Rhinocerebral zygomycosis
<i>Coccidioides immitis</i>	Meningitis

PARASITIC AGENTS

Organism	Clinical Manifestations
<i>Naegleria fowleri</i> , <i>Acanthameba castellani</i>	Meningoencephalitis
<i>Trichinella spiralis</i>	Meningoencephalitis
<i>Trypanosoma</i> species	Meningoencephalitis, sleeping sickness
<i>Toxoplasma gondii</i>	Encephalitis
<i>Plasmodium falciparum</i>	Cerebral malaria
<i>Taenia solium</i>	Central nervous system cysticercosis (neurocysticercosis)

CNS INFECTIONS

VIRAL AGENTS

DNA Viruses	Clinical Manifestations	RNA Viruses	Clinical Manifestations	Prion	Clinical Manifestations
Herpes simplex Types 1 and 2	Encephalitis, meningitis	Colorado tick fever	Encephalitis	Prion	CJD
Varicella-zoster	Encephalitis, meningitis	LaCrosse encephalitis	Encephalitis		
Cytomegalovirus	Encephalitis, meningitis	HIV	Encephalitis		
JC virus	PML	St. Louis encephalitis	Encephalitis		
		West Nile	Encephalitis		
		EEE, WEE, VEE	Encephalitis		
		Mumps	Encephalitis		
		Measles	Encephalitis		
		Rabies	Encephalitis		
		HTLV	Myelitis, myelopathy		
		Polio, coxsackie, echovirus	Myelitis, myelopathy, meningitis		
		LCMV	Meningitis		

URINARY TRACT INFECTIONS

BACTERIAL AGENTS

Organism	Clinical Manifestation	Organism	Clinical Manifestation
<i>Chlamydia trachomatis</i>	Urethritis	<i>E. coli</i>	UTIs
<i>Neisseria gonorrhoeae</i>	Urethritis	<i>Pseudomonas aeruginosa</i>	UTIs
<i>Klebsiella pneumoniae</i>	UTIs	<i>Proteus mirabilis</i>	UTIs
<i>Staphylococcus saprophyticus</i>	UTIs	<i>Enterococcus faecalis</i>	UTIs
<i>Mycoplasma genitalium</i>	Urethritis		

VIRAL AGENTS

DNA Viruses	Clinical Manifestation
Adenovirus type 11	Hemorrhagic cystitis
BK virus	Hemorrhagic cystitis (immunocompromised patients)

FUNGAL AGENTS

Organism	Clinical Manifestations
<i>Candida glabrata</i>	Cystitis

PARASITIC AGENTS

Organism	Clinical Manifestations
<i>Trichomonas vaginalis</i>	Urethritis
<i>Schistosoma hematobium</i>	Cystitis, hematuria, bladder carcinoma

SEXUALLY TRANSMITTED INFECTIONS OR RELATED GENITOURINARY TRACT MANIFESTATIONS

BACTERIAL AGENTS

Organism	Clinical Manifestations
<i>Chlamydia trachomatis</i>	Nongonococcal urethritis (NGU), cervicitis, pelvic inflammatory disease (PID), lymphogranuloma venereum (LGV)
<i>Treponema pallidum</i>	Syphilis
<i>Neisseria gonorrhoeae</i>	Urethritis, cervicitis, PID
<i>Mycoplasma genitalium</i>	Urethritis

VIRAL AGENTS

DNA Viruses	Clinical Manifestations	RNA Viruses	Clinical Manifestations
Human papilloma	Genital warts, anogenital cancer, cervical cancer, oropharyngeal cancer	Hepatitis C	Hepatitis, cirrhosis, liver cancer
Cytomegalovirus	Retinitis, pneumonitis, encephalitis	HIV	AIDS
Herpes simplex Types 1 and 2	Genital herpes, gingivostomatitis	HTLV	Adult T-cell leukemia, HTLV-1-associated myelopathy/tropical spastic paraparesis (HAM/TSP)
Hepatitis B	Hepatitis, liver cancer		
HHV-8 (KSHV)	Kaposi sarcoma		

FUNGAL AGENTS

Organism	Clinical Manifestations
<i>Candida albicans</i>	Vulvovaginitis

PARASITIC AGENTS

Organism	Clinical Manifestations
<i>Trichomonas vaginalis</i>	Vaginitis, urethritis, prostatitis
<i>Giardia lamblia</i>	Diarrhea
<i>Cryptosporidium</i> species	Severe diarrhea in AIDS patients

CONGENITAL INFECTIONS (INFECTION IN UTERO)

BACTERIAL AGENTS

Organism	Clinical Manifestations
<i>Treponema pallidum</i>	Congenital syphilis
<i>Listeria monocytogenes</i>	Fetal death, malformations

VIRAL AGENTS

DNA Viruses	Clinical Manifestations	RNA Viruses	Clinical Manifestations
Parvovirus B19	Fetal death, anemia	Rubella	Fetal death, malformations
Cytomegalovirus	Fetal death, malformations	HIV	HIV/AIDS
Varicella-zoster	Fetal malformations	LCM	Fetal death, malformations
		Zika	Fetal microcephaly and other brain defects

PARASITIC AGENTS

Organism	Clinical Manifestations
<i>Toxoplasma gondii</i>	Fetal death, malformations

Note:

TORCH is an acronym for pathogens that can cause congenital conditions (present at birth) if a fetus is exposed *in utero*: Toxoplasmosis (Toxoplasma *gondii*), Other (such as HIV, *Treponema pallidum*, *Listeria monocytogenes*, varicella zoster virus, parvovirus, LCM virus, Zika virus), Rubella virus, Cytomegalovirus (CMV), and Herpes simplex virus (HSV).

PERINATAL INFECTIONS (INFECTION DURING

DELIVERY)

BACTERIAL AGENTS

Organism	Clinical Manifestations
<i>Escherichia coli</i>	Neonatal meningitis
Group B streptococcus	Neonatal meningitis
<i>Listeria monocytogenes</i>	Neonatal meningitis
<i>Neisseria gonorrhoeae</i>	Neonatal conjunctivitis
<i>Chlamydia trachomatis</i>	Neonatal conjunctivitis, pneumonia

VIRAL AGENTS

DNA Viruses	Clinical Manifestations	RNA Viruses	Clinical Manifestations
Herpes simplex Type 2	Neonatal herpes	HIV	HIV/AIDS
Varicella zoster	Neonatal varicella		
Human papilloma	Laryngeal warts		
Hepatitis B	Chronic hepatitis		

FUNGAL AGENTS

Organism	Clinical Manifestation
<i>Candida species</i>	Neonatal oral thrush

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